SUPPLEMENT

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Section I.—Medicine.

(*Continued.*)

HYDATIDS OF THE HEART AND HYDATID EMBOLI.

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Mrs. S., *aetatis* thirty-eight years, was seen on December 12, 1914, with a right spastic hemiplegia.

She had been married for four years and had never been pregnant. Once since her marriage she had had a mild attack of pleurisy.

Except for this she had been in good health, till May 10, 1914. On that day she had "a funny feeling in her head" and soon became unconscious. She remained so for nine days and then was found to be suffering from right hemiplegia and aphasia. She gradually recovered her speech and power in the limbs to a certain extent, but the spasticity in the arm and leg remained and she wished something done for that.

She had never suffered from headache or vomiting, her sight was good and she had been able to do her own housework up till the time of the attack in May.

Her family history was very good. She had twelve brothers and sisters alive and in good health.

When examined there was found to be a partial right hemiplegia with much spasticity. Sensation was very little affected. No cardiac or pulmonary abnormality was detected. Her systolic blood pressure was 100 millimetres of mercury. The urine was normal. A Wassermann blood test did not yield a reaction.

The patient was taken to the Alfred Hospital and remained in much the same condition for a week. Then on seeing several doctors and students approaching her bedside, she became very agitated with much cardiac palpitation. She was unable to speak and soon became unconscious, both sides of the body twitching irregularly. The left plantar reflex was extensor. She remained unconscious, till her death two days later.

Post mortem examination showed:

(1) A hydatid cyst of the left ventricle of the heart which had ruptured into the ventricular cavity; this cyst contained several small daughter cysts.

(2) A large hydatid cyst in the right occipital lobe of the brain, containing daughter cysts.

(3) A hydatid cyst in the left middle cerebral artery. Apparently this had grown since its implantation. There was softening in the area of the brain supplied by the vessel.

(4) A hydatid cyst in the right middle cerebral artery which had recently blocked that vessel. There was no clotting beyond the cyst.

(5) Two small hydatid cysts in the spleen.

(6) A small hydatid cyst in each kidney.

There were fibrous calcareous patches in the lung, but no evidence of hydatid elements (A.V.M.A.).

Hydatid of the Heart.

The literature of hydatid of the heart is scattered and considerable.

Usually the condition is unsuspected and, as in the present case, is undiscovered until the *post mortem* examination.

The only report of the diagnosis of hydatid cyst of the heart during life, that I can find, is that by Dr. Humphrey Marten, in 1921 (1).

Hydatid of the heart has been reported in many journals and from many parts of the world. It occurs more frequently in the right side than in the left, as would be expected if blood borne (2). In all probability hydatid of the heart is mostly primary, even if cysts co-exist in other organs. Secondary hydatid cysts of the heart have occurred as emboli from the liver.

The pathology of hydatid of the heart may be summarized under the following headings.

Latency.

It may be found at *post mortem* examination of patients in whom neither the symptoms during life nor the mode of death could be correlated with its presence.

Fibrillation.

This was probably the cause of sudden death of the patient, whose case was described by Price in 1820 (3). A boy of ten became ill as he was walking home from school and died twenty minutes later. At the *post mortem* examination the pericardium was found adherent and in the muscle substance of the heart a large hydatid cyst was found. The report does not say what part of the heart was affected nor whether the cyst had ruptured. Evans (4) reports the case of a female, aged forty, who suffered from paroxysmal attacks of dyspnœa and pain in the left side of the chest. At the *post mortem* examination he found a globular unruptured hydatid cyst containing a number of daughter cysts in the apex of the right ventricle. Externally the cyst was adherent to the pericardium.

Rupture.

A frequent result of hydatid cyst of the heart is rupture, either into the pericardium or into the cavity of the heart.

Rupture into the Pericardium.

Usually sudden death follows rupture into the pericardium, but Dévé (5) collected three probable cases of

FIGURE I.

From a Photograph of Dr. Anderson's case of Hydatid Cyst of Left Ventricle (Museum of Pathology, University of Melbourne).

growth in the pericardial cavity after rupture and survival. Dévé and Jiron (6) report a case of a hydatid cyst of the heart complicated by secondary echinococcosis of the pericardium. Sudden death took place from rupture of one of the pericardial cysts into the left auricle.

Rupture into the Heart Cavity.

Death may be sudden or rapid from shock, intoxication or gross embolism. Wilks (7) reported the sudden death of a female, aged nineteen, in apparently good health. At the *post mortem* examination a hydatid cyst, the size of a billiard ball, was found free in the left ventricle. There were no daughter cysts. The cyst had shelled out from the inner wall of the apex of the heart and blocked the valve.

A case of a similar nature was reported by Kelly (8) of a boy aged ten, who died suddenly at work. Two weeks before, he had complained of slight pain in the chest. At the *post mortem* examination a ruptured hydatid cyst was found in the right auricle of the heart. Lining the right auricular appendix was a thin, still adherent sac with numerous daughter cysts; one of these, the size of a walnut, had escaped and, acting as a ball valve in the tricuspid orifice, prevented the passage of blood or of smaller vesicles into the right ventricle. The patient in this instance died of cerebral anæmia.

Instances of pulmonary embolism from hydatid of the heart were recorded by Rokitansky (9) and Budd (10) and by Howitt (11). Howitt's patient referred to by Allen (12) had a hydatid cyst in the right ventricle at the apex projecting into the cavity, full of small daughter cysts which had ruptured. Both lungs contained numerous hydatid cysts, the right more than the left, mostly contained in dilated branches of the pulmonary arteries.

Altmann (13) describes a hydatid cyst of the heart which caused cerebral embolism.

Dévé (14) reports about ten cases in which the same cyst of the heart had burst two or three times in succession; rupture into the pericardium has usually been unique, into the cavity has often been repeated.

Degeneration, Calcification and Absorption.

Hydatid cysts have been found at *post mortem* examinations on patients who have died suddenly or from an intercurrent disease in which the cysts were partially absorbed or degenerating. Rokitansky (9) Peacock and Hicks (15), Goodhart (16) have described such degenerating cysts; death occurred suddenly. Figure III. shows a degenerating cyst of the heart wall, from a specimen in the Museum of Pathology, Melbourne University.

Suppuration.

This will almost certainly give rise to death by septic poisoning or emboli.

HYDATID EMBOLI.

The most complete work on this subject has been published by Dévé (17) in an important series of articles on hydatid grafts; he has collected a large number of cases from the literature. The embolus may occur in the heart, originating from the liver (18) or from the right auricle (8). Secondly, emboli may occur in arteries of the lung (11), (12), brain (13), and other parts, such as the iliac

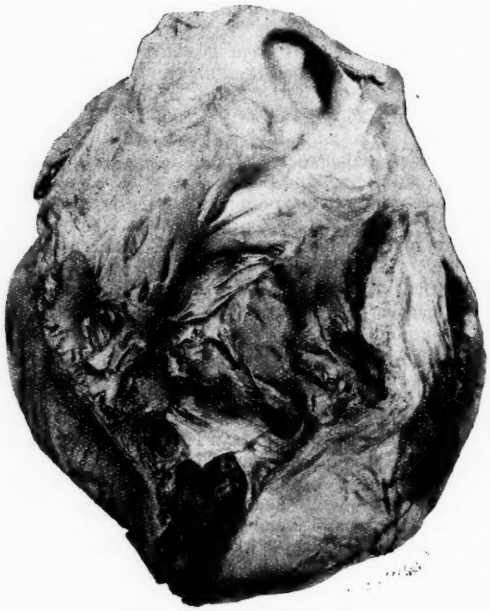

FIGURE II.

Hydatid Cyst of the Apex of the Left Ventricle with Daughter Cysts (Museum of Pathology, University of Melbourne).

arteries (19). These are gross emboli of daughter cysts, originating from rupture of the hydatid in its original site; but Dévé has shown experimentally that "metastatic" emboli may occur, that is, scolices getting into the circulation may be carried to other organs of the body and settling there may develope into secondary cysts.

It is generally accepted that the hydatid embryo emerges from the ovum after solution of the hard outer membrane by the digestive juices and piercing the wall of the intestinal tract is carried by the blood to the brain where it settles and grows to be the primary hydatid cyst of the brain. As infection takes place more usually in the young and growing, hydatid cysts of the brain give rise to early symptoms of pressure; hydatid tumours of the brain are found more usually in young people. Dévé and Dumont (20) quote from Argentine statistics that 87% of brain hydatids occur in children under fifteen years of age.

Of cerebral emboli in the generally accepted sense, that is whole or ruptured daughter cysts plugging the cerebral arteries, we have been able to collect only three cases other than that described above. In these three the patient did not survive.

McCall Anderson (21) reports the case of a healthy quarryman aged thirty-five, who complained suddenly of severe abdominal pain and loss of power in the right arm and leg. He was pulseless and collapsed on being brought to hospital, his heart beating very feebly and rather slowly. The face and tongue were normal. Pupils were equal and reacted to light. Later, the right side of the face and tongue, right arm and leg became completely paralysed and the man gradually became more comatose and died. The *post mortem* examination revealed the wall of a ruptured daughter cyst plugging the internal carotid artery in the cavernous sinus. There were more cysts in the aorta and iliac arteries from a pea to a pigeon's egg in size. In the interventricular septum of the heart there showed the cavity of a hydatid cyst which had ruptured into the left ventricle.

Dähnhardt (22) records the case of a twelve year old girl who complained of severe headache in school and vomited. During the following night the patient had a convulsion and became comatose with pin-point pupils and absence of all reflexes. The left side of the body and limbs was colder and more flaccid than the right. Death occurred five hours later. At the *post mortem* examination hæmorrhage into the right hemisphere and ventricles was found, which had followed embolism of the left cerebral arteries with echinococcus daughter cysts. Examination of the rest of the body was not permitted, but it was presumed that the emboli had come from a ruptured hydatid cyst of the left ventricle of the heart.

Altmann (18) published the history of a young female who complained of headache; sudden death occurred next day following a general convulsion while at work. At *post mortem* examination the posterior wall of the left auricle was seen to be occupied by a hydatid cyst the size of an orange which had ruptured into the auricle. The left external (?) carotid was blocked by a daughter cyst at its entrance into the cranium. The right carotid and vertebral arteries were patent. The vessels in the neck could not be examined (S.W.P.).

The difficulty of diagnosis in such a case as that recorded is obvious and the practical importance probably not very great. It may be well, however, to bear in mind the possibility of such a condition as hydatid disease in an apparently inexplicable cardiac condition, which may perhaps show suspicious evidences of hydatid on radiographic examination.

The performance of the hydatid complement fixation test may give a clue to the real nature of the condition.

Then, too, the possibility of embolic conditions supervening on hydatid disease in any part of the body has to be remembered.

It is to Dévé, of Rouen, and his pupils that we owe most of our knowledge of this condition; he states that he knows of over one hundred cases in which secondary echinococcosis, embolic and otherwise, has occurred.

FIGURE III.
Degenerating Cyst of the Heart Wall (Museum of Pathology, University of Melbourne).

His prophylactic maxims are worth quoting (23): (i.) Endeavour to recognize hydatid cysts betimes, seek them in adolescents and in children; (ii.) never make either exploratory or therapeutic punctures into a hydatid cyst; (iii.) operate as soon as the cysts are recognized; (iv.) operate correctly, striving to avoid insemination of living echinococcus germs which is a possible cause of hydatid relapse after operation (A.V.M.A.).

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"INSULIN" IN GENERAL PRACTICE.

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As it would obviously be quite hopeless to discuss in the time allowed for this paper all the interesting facts that have emerged from the use of "Insulin" in the treatment of diabetes, I have decided to confine my remarks to a discussion as to whether it is possible for the general practitioner who has not the facilities at hand for making blood sugar estimations or doing accurate quantitative analyses of the sugar output, to carry out treatment satisfactorily by this new and very wonderful organic extract.

Personally, I think it is quite possible, provided only that the necessary trouble be taken to handle the case dietetically, as well as medically; and I would like to say here and now that nothing in the whole course of my professional experience has given me so much mental satisfaction as I have had in the treatment of diabetics during the last six months since "Insulin" was made available by the Commonwealth Serum Laboratories. Further, I would like to pay a tribute of praise to Dr. Penfold, Dr. Morgan and their working staff for the rapidity with which they have succeeded in making available supplies of "Insulin," fully potent and free from any products tending to cause disagreeable reaction. I do not think that too much credit can be given for the splendid work they have accomplished.

To the practitioners I would say that, if you are proposing to use "Insulin," you must first make quite sure that your case of glycosuria is really a case of diabetes. That is not always easy, but if the patient has had typical symptoms, thirst, polyuria, loss of weight, *et cetera* or if you know there has been glycosuria and coma is threatening with diacetic acid in the urine, you need not hesitate in your use of "Insulin."

It is in the mild cases that doubt arises, cases where perhaps there are only traces of sugar, with no symptoms or even fairly large amounts of sugar with no symptoms. These patients may not be really diabetics at all and before using "Insulin" on them careful blood sugar tests ought to be done or you may readily run into disaster.

A man came to me recently from Tasmania for treatment by "Insulin." He had had starvation treatment by a leading London specialist without success and, though his glycosuria was of years' standing, he appeared to be in perfect health. His blood sugar was only 0.09% and after fifty grammes of glucose it went only to 0.13%. "Insulin" in that case would certainly have led to a hypoglycæmia, so you need to be careful in these apparently mild cases. Maclean recommends that in the absence of blood sugar estimation, a dose of fifty grammes of glucose may be given fasting and if at the end of two and a half hours only a trace or no sugar is present in the urine, the patient should not be treated with "Insulin," he may be a renal diabetic.

But there are many cases in which there is no doubt at all and these come into the purview of the general practitioner. I can see no reason why they should not be treated by the general practitioner.

First and foremost patients with threatened diabetic coma are always seen first by the general practitioner and my present feeling is that diabetes should never be allowed to drift into coma.

If your diabetic patient shows signs of drowsiness and lethargy, with air hunger and a marked ferric chloride reaction in the urine you should at once start the use of "Insulin." I would at once give such a patient ten units, buffered by a tumbler of orange juice. As you do not know the blood sugar contents and as the glycogen reserves in the liver may have been all used up (especially in wasted patients) you can make yourself safe by giving a good dose of rapidly absorbable carbo-hydrate and this you get in orange juice. It will, of course, possibly increase the blood sugar, but you need not worry on that account.

What you are after is to get rid of the acidosis and your "Insulin" will so help the utilization of the blood sugar by the tissue cells, as in some mysterious way at the same time it will help the metabolism of the fats and their poisonous products. Having given your first dose, in two hours get a specimen of urine. If it still contains sugar, with or without diacetic acid, give another

dose of "Insulin." As long as diacetic acid persists, you must go on with your "Insulin," possibly every two hours, but if the patient is obviously improving, every four hours may suffice. Give your orange juice or some well boiled oatmeal with each dose till you get rid of your diacetic acid. This may occur within twenty-four hours. Then you have to go on to clear out the sugar and now begins the problem of dieting. You must take the trouble to learn the approximate values of the most important food stuffs and must gain some facility in calculating diets in terms of grammes of carbo-hydrate, protein and fat. It is all very simple, if you use the card tables as given above.

If you are not prepared to take this trouble, then you cannot hope for any success in the treatment of diabetics, either with or without "Insulin," for the use of "Insulin" will not allow you to dispense with the necessity for careful dieting.

Having rescued your patient from the threat of coma, I think the best plan then is to put him on a calculated low maintenance diet at first, *id est*, a diet which will yield just sufficient calories to keep a patient at rest in bed in a condition of slightly lowered basal metabolism and, of course, as a counsel of perfection in nitrogen balance, but you will have to ignore that.

Such a diet can be accurately calculated by taking account of the patient's age, sex, height and weight and we have nomographic charts for that purpose.

But, for practical purposes you can take twenty-five calories per kilogramme of body weight as a working figure and then the equations

$$C = 0.024\ M - 0.41\ P.$$
$$F = 4\ C + 1.4\ P.$$

when C = carbo-hydrate, M = total calories required, P = protein and F = fat.

If you fix your protein as 0.66 gramme per kilogram of body weight, you will be safe and you can then calculate a diet for carbo-hydrate, protein and fat which will give you your requisite calories and be so balanced as to check the tendency to ketogenesis.

You have now to calculate the glucose value of that diet (G).

$$G = C + 58\%\ P + 10\%\ F.$$

and, as our unit of "Insulin" may roughly be taken as capable of metabolizing two grammes of glucose, you can calculate how much "Insulin" you require to deal with your diet.

Suppose G = 80, then give forty units of "Insulin" in divided doses before each meal, say four meals a day and ten units a quarter of an hour before each. Test the urine two hours after each meal: if it is sugar free, drop your next dose of "Insulin" and see what happens. If sugar recurs, try six units as the next dose and so on, till you find out the amount required to keep sugar free all day.

Your forty units may only be enough to metabolize the potential glucose of your food, but not the accumulated sugar excess in the blood and then you must carefully increase your dosage, until you get urine sugar-free and the blood sugar approaching normal. The patient is not always satisfactory when merely the urine is sugar-free and it is desirable at this stage to secure a blood sugar estimation, for often the high blood sugar persists and more "Insulin" is required to control this. Many failures in treatment have occurred from failure to recognize this point.

If all is going on well, you can gradually increase the carbo-hydrate and probably in many cases reduce the "Insulin."

At all times you must be on the look out for symptoms of hypoglycæmia. These usually will come on one to one and a half hours after the injection. If the blood sugar has fallen to about 0.07, the patient will probably complain of great hunger and a peculiar sense of nervousness and impending trouble. Chills and flushes often occur, but the most characteristic sign is localized or even profuse general sweating. Sometimes there is a sense of tremor and even actual tremors and, if the blood sugar falls too low, you may get mental excitement and even convulsions and coma, followed by death in a severe case.

Your nurses and patients should be told of all this and be instructed to take at once a tumblerful of orange juice with some glucose dissolved in it, if the condition seems severe. In half an hour comfort will have returned. If coma should have supervened, you must give the dextrose intravenously. I saw one case of this and the recovery was dramatic; the patient suddenly awakened and wanted to know what all the fuss was about.

In well nourished patients, with probable storage of glycogen in the liver, an injection of one cubic centimetre of 1 in 1,000 "Epinephrin" solution will liberate the store of glycogen to the blood and hasten recovery from hypoglycæmic coma.

The following case will illustrate many of the above points.

T.McD., *aetatis* 21 years, has had diabetes for over a year. On August 19, 1923, he began to get drowsy and was given three units of "Insulin" which was repeated that evening. Next day the drowsiness increased, intense headache and vomiting supervened and he became extremely ill. He had some "Insulin" during the day. I saw him in the evening and gave six units. He was then very drowsy, suffering severely from headache and vomiting, but was able to swallow. His urine was loaded with sugar and diacetic acid. Orange juice was given along with the "Insulin" and three doses were given during the night. Next morning he was decidedly better; he had slept a little, was less drowsy and had less headache.

During the day "Insulin" was given three or four times, six units, and some oatmeal was given as well along with broth and white of egg. He continued to improve and on the following day diacetic acid had disappeared from his urine. The blood sugar was over 0.2%.

He was removed to hospital August 25, 1923, and put on a diet of twenty-two grammes of carbo-hydrate, twenty-four grammes of protein and twenty-seven grammes of fat or 427 calories with glucose value 37 and ten units of "Insulin" before each meal. Sugar was still present and some diacetic acid. His food was rapidly increased until in a few days he was on twenty-nine grammes of carbo-hydrate, fifty-eight grammes of protein and eighty-five grammes of fat, equivalent to 1,113 calories with a glucose value of 70. The urinary sugar was distinctly less.

On August 31, 1923, there was no diacetic acid, the sugar was less; he was receiving the same "Insulin" doses. We were now at the stage when diacetic acid had gone and

the sugar obviously lessening and my orders were that if the sugar disappeared, the "Insulin" dose after one meal should be omitted.

He had been complaining for some days of pain in the left groin and a swelling had developed and pyrexia at night. This inflammatory factor sent his sugar up and the diacetic acid returned. Later, he became drowsy again, refused to take his food, complained of headache and a dry tongue and had much pain. The diacetic acid was again plentiful. He was then given thirteen units three times a day and later sixteen unit doses and for a few days very little food.

On September 14, 1923, he had sixty-three units between 7.30 a.m. and 8 p.m. with only oatmeal and orange juice with the white of four eggs. He looked at one time as if going into coma, but next day the report was "no diacetic almost all day" and only slight diacetic about midday. The food was increased and thirty-eight units of "Insulin" were given. His food was rapidly increased again till on September 19, 1923, he had twenty-four grammes of carbo-hydrate, sixty-three grammes of protein and fifty-one grammes of fat equivalent to 807 calories with a glucose value of 65; he was receiving fifty units and the blood sugar was 0.194%. No blood sugar test had been done in hospital till this day. We had controlled the situation by constant observation of the urinary sugar and diacetic acid.

The diet was now increased to 1,593 calories with a glucose value of eighty-two and were giving fifty units of "Insulin" by September 24, 1923, a trace of sugar only and no diacetic acid were reported.

On September 29, 1923, the urine was sugar-free all day on sixty units and a glucose value of 78. "Insulin" was decreased to fifty units daily and on October 2, 1923, fifteen grammes (half an ounce) of bread given and one "Uneeda" biscuit yielding 1,647 calories with a glucose value of 100 kept his urine sugar free while he had forty units of "Insulin."

On October 3, 1923, twelve units of "Insulin" in two doses were given and there was no sugar.

On October 5, 1923, he had six units of "Insulin" before breakfast and three units before lunch. His diet was as follows:

570 grammes (20 ounces) of 5% vegetables.
57 grammes (2 ounces) of 15% apple.
14 grammes (½ ounce) of oatmeal.
28 grammes (1 ounce) bread.
One "Uneeda" biscuit.
85 grammes (3 ounces) of meat.
Two eggs.
57 grammes (2 ounces) of bacon.
57 grammes (2 ounces) of butter.
57 grammes (2 ounces) of cream.
28 grammes (1 ounce) of sardines.

The urine was clear all day, there was no sugar, no diacetic on nine units. Can anything be more impressive than this case? He was twice rescued from impending coma; he passed through a severe inflammatory attack in which he suffered severe pain. He had to get morphine several times and, as soon as the attack had subsided, his symptoms began to clear up so rapidly that his "Insulin" was decreased at once. Only one blood sugar estimation was done, and the whole case successfully controlled by constant watchfulness of urinary findings.

He had the advantage of the great skill of the Mena House staff and of the most careful control of his diet and it was only by reason of this that so splendid a result was obtained. At no time did we get any sign of hypoglycæmia.

Up to the time of writing this paper I have treated three other patients with similarly threatened coma on similar lines with complete success.

But what of the case of complete coma? Let the following tell its own story.

This contained sixty-two grammes of carbo-hydrate, seventy-three grammes of protein and one hundred and thirty-eight grammes of fat, and yielded 1,786 calories with a glucose value of 117 grammes.

I saw an old lady of fifty-six years at 11 p.m., with Dr. Disher. She had gone into coma about 5 p.m. and when I saw her was completely comatose, almost pulseless, with a dry tongue and exceedingly minus tension eyeballs. We gave her ten units of "Insulin" every hour for three doses; then every two hours, with as much orange juice as we could get her to swallow and at 8 a.m. she was talking.

I saw her again at 10.30, and she was well awake and mentally quite alert, taking notice of ordinary conversation by the bedside.

Can you wonder that my feeling is that no patient with coma should be allowed to die after such an experience, if we are only bold enough to push the use of "Insulin."

Subsidiary treatment should be warmth, administration of fluid by mouth, rectum or even intravenously, containing soluble dextrose, and no fat for a few days. Digitalis and strychnine may also be given if thought necessary.

Another type of case that you should be able to treat successfully is the acute diabetes so often seen in young adults. The following is the type of such a case.

R.G., *aetatis* 20 years, was seen with Dr. A. M. Wilkinson on September 6, 1923. Two weeks previously he suddenly developed thirst and polyuria and his urine was found to be loaded with sugar, but no diacetic acid. Here was a case of some sudden pancreatic upset. If we could rest the damaged pancreas, we might hope for considerable, if not complete recovery of function. He was put on a gradually decreasing amount of food and on the fourth day his urine cleared on a diet with a glucose value 15 G. We decided then to put him at once on a diet of forty grammes of carbo-hydrate, fifty grammes of protein and one hundred and twenty-four grammes of fat with a glucose value of seventy-nine grammes.

As he had metabolized about fifteen grammes of glucose, that left sixty-four grammes for the "Insulin" to deal with and we calculated that thirty units should keep him sugar-free and give his pancreas almost complete rest from work. This happened as we had predicted; no sugar appeared and he went on till the ninth day. This showed also that Commonwealth "Insulin" was fully potent and fulfilled its calculated value.

On the tenth day there was added to his diet twenty-eight grammes (one ounce) of bacon, fifty-seven grammes (two ounces) of potato, fourteen grammes (half an ounce) of bread, twenty-eight grammes (one ounce) of extra meat and the same dosage of "Insulin." It was obvious that he needed some increase of food, as he had had slight sweating and nervous anxiety which was relieved in half an hour by orange juice with no return of sugar. His diet now yielded 1.818 calories and contained sixty-two grammes of carbo-hydrate, sixty-eight grammes of protein and one hundred and forty-four grammes of fat with a glucose value of 115 grammes. "Insulin" accounted for sixty grammes of glucose, so his own tolerance was now fifty-five. He was then given six, ten and six units and kept sugar-free.

except for a trace after breakfast, hence the ten units midday dose.

On the fourteenth day three doses of six units kept him sugar-free on a diet of sixty-one grammes of carbo-hydrate, sixty-two grammes of protein and one hundred and forty-five grammes of fat, providing a glucose value of 110, with potato, bread 5%, 10% and 15% (apple) *et cetera.*

On the seventeenth day two doses only of six units kept him sugar-free on the same diet. His diet was then increased to 1,857 calories with a glucose value of 116 and he went home and has controlled this with two injections of six units daily. I saw him on November 5, 1923, looking in perfect health, feeling extremely well and I hope that his pancreas may have recovered most of its function.

In the whole course of the case only one blood sugar estimation was done to see what was the reading after the hypoglycæmic reaction. It was 0.109%. Could anything be more encouraging than the treatment of such a case?

Take another type of case, where after prolonged dietetic treatment the patient can just about keep sugar free on a rather restricted diet, but as soon as any attempt is made to increase the food intake, sugar appears.

As an instance a patient on a diet of fifty grammes of carbo-hydrate, sixty-six grammes of protein and one hundred and thirty-two grammes of fat, with a glucose value of 101, showed traces of sugar at 10.30 a.m. and 2.30 p.m., but was clear at 7.30 p.m. Her diet was not quite adequate for her requirements, so we put her on seventy-one grammes of carbo-hydrate, seventy grammes of protein and one hundred and thirty-two grammes of fat, with a glucose value of 124, yielding 1,752 calories, giving her the bulk of her carbo-hydrate at midday (one hundred grammes of spinach, one hundred grammes of celery, sixty grammes of potato, one hundred grammes of apple, fifteen grammes of bread and fifty grammes of onion) with meat, cream, butter and ten units of "Insulin" fifteen minutes before the midday meal. The result was not a trace of sugar at 2.30 or at 7.30 p.m. or at 7.30 a.m. next morning.

The psychological effect of one good meal a day with two lighter meals counts for a great deal. The patient is well satisfied and the taking of one injection of "Insulin" daily is easily managed. I am sure that many mild cases can be safely treated on these lines and have already had several successfully so treated.

Time does not permit me to tell of many other cases, but when one has seen people with severe diabetes of long standing, whose outlook on any kind of dietetic treatment was absolutely hopeless, restored to a measure of health and comfort by the judicious use of "Insulin," can you wonder that one feels this to be the greatest discovery in modern medicine? Whatever the ultimate result may be, there can be no doubt as to the startling nature of the immediate benefit and there is surely good reason to hope that in very many cases permanent good will accrue. Admittedly, the treatment needs care and a good deal of common sense and satisfactory results will only be obtained by those who will take the trouble to master the essential principle of dietetics. If you will not take the trouble to spend a few hours in studying the value of food stuffs, you ought not to be allowed to use "Insulin," but if you will, I can only say that great will be your reward.

"INSULIN."

By F. G. Morgan, M.B., Ch.B. (Melbourne),
Commonwealth Serum Laboratories, Royal Park, Victoria.

Owing to the presence of Dr. Penfold and myself at other meetings of the Congress on Wednesday morning, it was found impossible to take part in the discussion concerning "Insulin" which followed the paper by Dr. J. F. Wilkinson. By the kind permission of the President a few minutes have been allotted to me in which to refer briefly to certain aspects concerning the distribution and use of "Insulin" prepared by the Commonwealth Serum Laboratories.

The following points were raised at Wednesday's meeting:

(1) The expensive nature of "Insulin," (2) the instability of the product prepared by the Commonwealth Serum Laboratories.

There are two factors amongst others which are responsible for the expense entailed in treatment with "Insulin." They are: (i) The price of the unit and (ii.) the quantity of the preparation required to be used.

The price of "Insulin" is fixed according to a definite policy which takes into consideration the capital expenditure, the current expenditure and the output of "Insulin." When the receipts from sales exceed the current expenditure including the gradual repayment of capital expended, the price of the unit is reduced accordingly. Following this policy the price of "Insulin" has been reduced in the past from five pence a clinical unit to four pence and again from four pence to three pence. A further reduction will be made within the next fortnight.

Increased production and sales in the future will enable us to make further reductions, in continuation of the policy of issuing this product at cost price.

In reviewing the case records of diabetics supplied to the Director of the Commonwealth Serum Laboratories, it became evident that in certain cases in which diabetics were receiving particularly large doses of "Insulin," a considerable economy in "Insulin" could be effected if the diet were balanced according to the formulæ of Wilder or of Campbell. As you know diets calculated upon a basis of these formulæ allow a much more liberal amount of fat although the ketogenic and anti-ketogenic substances are so balanced that ketosis is unlikely to develope. I believe that these points have been dealt with by speakers at Wednesday's meeting, but at the risk of recapitulation I would like to cite an example. One patient who was receiving a mixed diet containing carbo-hydrate eighty grammes, protein eighty-six grammes and fat one hundred and sixty-two grammes with a glucose producing value of one hundred and forty-six was receiving eighty units of "Insulin" per day. This diet supplied total calories of 2,122. With a more liberal allowance of fat and less carbo-hydrate with one gramme of protein per kilogram of body weight, a diet can be constructed with the same glucose producing value to supply approximately 4,500 calories per day. Thus a very considerable saving in the amount of "Insulin" to be used can be effected, so that the physician himself is partly responsible for the expense involved in a large dosage of "Insulin."

The records supplied to us support the contention that when a suitably balanced diet is given on the lines mentioned and combined with "Insulin" treatment, a considerable economy in the use of "Insulin" will be effected. The results of treatment with a high fat diet *plus* "Insulin" compare very favourably with those patients who have been receiving an unduly liberal allowance of glucose expressed in terms of the glucose producing value of the diet. "Insulin" will insure that the glucose is utilized in sufficient amount to prevent ketosis.

According to the press reports certain speakers made reference to the instability of the Commonwealth Serum Laboratories "Insulin." We knew in the early months of manufacture of this product that certain batches unaccountably and rapidly lost potency, but during the last four months or so we were given to believe by clinical reports received and by our own animal experimentation that the "Insulin" was retaining its potency very well indeed. We should like to know if the batches of "Insulin" that were referred to as being inert, were some of the "Insulin" prepared in the early stages of manufacture or whether they belonged to the later period. We would also consider it a favour if those physicians who have complaints to make concerning the potency or any other quality of "Insulin," were to communicate the same to the Laboratories, so that steps could be taken to remedy any defect. I should like to quote a few examples of testing carried out by ourselves to show that "Insulin" prepared by us was reasonably stable.

Batch No. 33 was passed through the Pasteur F. candle on September 10, 1923: In 0.5 cubic centimetre of this preparation there were three clinical units or one rabbit unit. On October 9 the same preparation contained one rabbit unit in 0.5 cubic centimetre. On October 17 and 22 this batch was still of that strength. No loss of potency had occurred over a period of six weeks' storage at 6.6° C. (44° F.).

Another batch was sent to Brisbane by post, was kept there for a period of three weeks, and then returned to the Laboratories, where it was kept at 6.6° C. (44° F.) for a further period of seven days. It was tested for potency and found to be up to full strength. It was then placed in the hot room at 37° C. for a period of ten days, when it was retested and found to have lost approximately 30% of its potency. Thus, after the severe test of 37° C. in the hot room for ten days, only about 30% deterioration in potency had occurred. It is our practice to forward fresh weekly supplies to every practitioner using this product. It is thought that by this means the deterioration which slowly occurs, will have little effect and the patient will always receive "Insulin" up to the full strength.

Advices received from Wellington, New Zealand, show that there is little difference to be detected between the "Insulin" supplied them from Toronto, Canada and the supplies forwarded from the Commonwealth Serum Laboratories, judging from the clinical results. "Insulin" prepared at the Commonwealth Serum Laboratories is made by the method of Doisy, Samogyi and Shaffer, by which procedure the purest form of "Insulin" is obtained by the methods known at the present day. One-quarter of a milligramme of the dried substance will contain three clinical units or one rabbit unit.

The clinical records supplied to us invariably show that the patients have been benefited by treatment with Commonwealth Serum Laboratories "Insulin." Diabetics have been restored from a condition of coma or severe acidosis and patients with severe diabetes who were steadily going downhill, have been placed upon a satisfactory footing.

Those members who are intending to make a visit to the Laboratories this afternoon, will have an opportunity of seeing in detail the preparation of this interesting product.

PROFESSOR A. E. MILLS said that dietetics must remain the foundation of treatment in diabetes. If "Insulin" was to be brought into general use, it would have to be possible to use it without making blood sugar estimations. A gradually increasing dose might be given, except when acidosis was impending. He did not think an excessively low diet was necessary as the patient then fed on his own fats and tissues. He did not see why more sugar should be given with "Insulin" when hyperglycæmia already existed. This did not apply to patients with ketonuria. He would regard two or three units as a small dose and this should be gradually increased. Pressure should be brought to bear on the Federal Government to lower the price of "Insulin"; at its present price it was impossible for poorer people to obtain the benefits of "Insulin."

DR. J. MACDONALD GILL agreed with all that Dr. Wilkinson had said, but felt that it was difficult to do without blood sugar estimation. He discussed the possibility of establishing permanent tolerance and the dosage. Finally he suggested that the Commonwealth Government should be approached and asked to remove the duty on imported "Insulin."

DR. A. R. SOUTHWOOD said that the cost of "Insulin" was a bar to its extended use especially among the poorer classes. The cost of one ampoule (ten clinical units) from the Commonwealth Serum Laboratories was said now to be two shillings and sixpence. In Adelaide the University authorities were manufacturing "Insulin" for the use of the local practitioners and the cost to the patient was approximately one shilling per ten clinical units. At that price the expenses of manufacture were wholly covered. Professor Brailsford Robertson hoped to reduce the cost still further by improving the methods of manufacture.

DR. G. R. WILLCOCKS asked Dr. Wilkinson for information regarding the lasting properties of the Commonwealth Laboratories "Insulin." In Sydney it appeared that this "Insulin" lasted only one week and it would be of interest to the profession generally to know whether this impression had been confirmed by other workers.

SIR HENRY MAUDSLEY agreed that some representations should be made regarding the reduction in the price of "Insulin." It now appeared that estimation of the blood sugar was not so important if reasonable care were taken. He had little doubt that in time "Insulin" would be prepared synthetically.

DR. H. N. BUTLER said that he had recently had two patients under treatment by "Insulin" for six weeks; one of them had received sixty units per day. Both had been kept on a strict diet and although there was still a small trace of sugar in the urine, diacetic acid and acetone had cleared away. The reason for the necessity of the large doses might have been that in the time taken for delivery the "Insulin" lost considerably in potency. Were these doses of "Insulin" in the two individuals mentioned to be kept up for the rest of their lives in order that they might take a little more food and have a little more comfort or should not "Insulin" rather be looked upon as a drug which was to be used in times of emergency such as threatened coma?

DR. C. T. C. DE CRESPIGNY described an experiment for the oral administration of "Insulin" suggested by Professor Brailsford Robertson. One gramme of a specially prepared charcoal of a known high adsorptive power had been administered to a patient who had had no food since 5 p.m. on the previous day. One hour later four (new style) "Insulin" units had been given orally. After the lapse of

another hour a meal containing five grammes of carbohydrate had been given. There had been no effect on the blood sugar and no glycosuria had been produced. His experience with the "Insulin" prepared at the Bio-chemical Department of the University of Adelaide was that it remained potent when kept cool for about one month.

Dr. J. F. Wilkinson in reply said that he did not undervalue blood sugar estimations; in fact it was a great comfort to have them. He wanted to show, however, that with care "Insulin" could be used without such methods.

With reference to dosage, Dr. Wilkinson expressed the opinion that the dose of "Insulin" should be calculated according to the glucose value of the food and advocated that a diet ample for the metabolic requirements of the patient should be given whenever possible. Of course some patients were so ill that they could not at first take this amount, hence the small food supply of the boy quoted and criticized by Professor Mills.

The cost of "Insulin" was too high and the meeting might well urge the Government to try and reduce that cost. In his experience "Insulin" manufactured at the Commonwealth Serum Laboratories remained potent for at least four weeks.

ANAPHYLAXIS AND ITS RELATION TO THE DIAGNOSIS AND TREATMENT OF HAY FEVER AND ASTHMA.

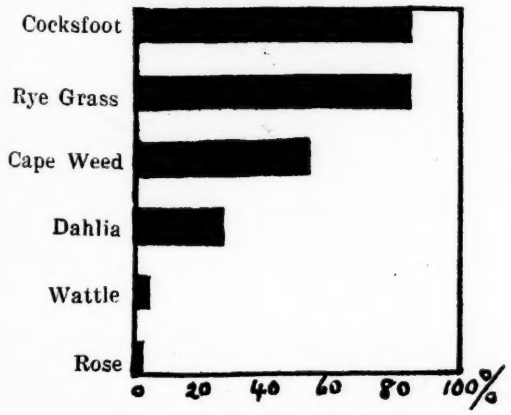
By L. A. Ivan Maxwell, M.D., M.Sc.,
Senior Lecturer in Physiology, University of Melbourne.

The results of modern investigations into the ætiology of hay fever and asthma tend to indicate that these conditions should be classed as examples of anaphylaxis. However, some writers, especially those in America, maintain that in these disorders there is no antigen-antibody relationship such as exists in anaphylaxis and they prefer to use the word "allergy" to indicate human protein hypersensitiveness.

In previous communications the writer has referred to the experimental method of producing anaphylaxis and to the theoretical interpretation of the cause of the condition.

Hay Fever.

The term hay fever as commonly used is inaccurate and misleading. The name was originally introduced to indicate the rhinorrhœa, sneezing and irritation of the eyes which occurred in certain persons as the result of the action of pollen from meadow or grass hay.



GRAPH.
Relati[illegible]ation Factors of Hay Fever.

Since then it has been used in a more comprehensive sense, including the condition of patients with similar symptoms to those described, but in whom the attacks were caused by the presence of certain animals, the taking of certain foods or by the irritating action of bacteria growing on the nasal mucus membrane.

The true seasonal type of hay fever, due to the irritation of pollen proteins, will first be discussed.

In Victoria grass hay is not frequently made, but rather oaten and wheaten hay. Prior to and during the hay making period various grasses pollinate and these are largely responsible for hay fever, especially rye grass, cocksfoot and prairie grass, and to these names should be added cape weed, which is a member of the natural order *Compositae*. Less frequent causative factors are canary grass, Yorkshire fog, couch grass, sorrel, Iceland poppy, sweet pea, cosmos, dahlia, wheat, oats and barley grass.

Table I.

Pollinating Period of Chief Plants Causing Hay Fever.

Plant.	Period of Pollination.	Plant.	Period of Pollination.
Meadow Grass	July to December	Cocksfoot	October to November
Tall Meadow Grass	July to December	Cape Weed	October to December
Yorkshire Fog	September to November	Sorrel	October to January
Rye Grass	October to November	Cosmos	February to March
Prairie Grass	October to November	Dahlia	March to April

Anemophilous plants are by far the commonest cause of hay fever, but in dry, hot weather entomophilous plants may be a potent factor.

Diagnosis of the Cause of Hay Fever.

This is accomplished entirely by cutaneous tests of which there are two varieties: (i.) The scratch test and (ii.) the intradermal test.

These tests have been described in a previous paper.

Treatment.

The nature of the pollens causing the hay fever having been determined, the next procedure is to attempt desensitization by graded doses of pollen extract using solutions of 1 in 20,000; 1 in 2,000; 1 in 200 and finally 1 in 20, as described in a previous communication. Many patients exhibit similar sensitization and the same pollen extracts can be used for all such cases. This saves a considerable amount of time in the preparation of the extracts.

Desensitization in patients must be attempted with due regard to the dangers associated with an overdose of the extract. Cooke reported constitutional reactions in fifty-one persons out of a total of four hundred and fourteen therapeutically injected with protein extracts. The constitutional symptoms may occur within a few minutes of injection or be delayed for several days. The symptoms include lachrymation, conjunctival injection, rhinorrhœa,

asthma, urticaria, œdema and erythema. These general reactions are mentioned so as to warn clinicians of the danger attached to therapeutic injection in highly sensitized persons. If very weak solutions are used to commence the injections and if the increase at each injection is very gradual, then the danger is reduced to a minimum; but, of course, the desensitization process takes longer and this should be explained to the patient.

Pseudo-Hay Fever.

In this condition the patient may complain of symptoms identical with those of true hay fever just described, but the ætiological factor is not pollen and the attacks are not seasonal, therefore, it is perhaps best to discuss these cases separately.

In many of these patients there is some septic focus in the nose or accessory sinuses and this apparently is a considerable factor in determining their symptoms.

In addition to sepsis there are many other irritants which cause pseudo-hay fever. The dandruff of animals, especially horses, may produce such symptoms, with or without causing the more serious asthmatic attacks.

The following case illustrates such a condition.

J.K., aged six years, has sneezing, rhinorrhœa and lachrymation in the presence of horses. Cutaneous tests revealed sensitization to horse dandruff and to graminaceous pollens, but the hay fever symptoms occurred even in the depth of winter if the child handled a horse. In the winter months, of course, grass pollens are not a causative factor. This child's brother was a horse asthmatic.

The dandruff of other animals, such as cats, dogs, rabbits, may cause pseudo-hay fever. Recently Coca described cutaneous tests obtained by extracts made from the dust of a patient's room. This dust caused pseudo-hay fever, but the exact constituent of the dust responsible for the positive cutaneous test has not been determined.

Foods are also regarded by some as being responsible for pseudo-fay fever and it is quite possible that foods which cause urticaria, may affect the mucous membrane of the nose.

With such a heterogeneous group of ætiological factors it is not surprising to find that positive cutaneous are far less frequent than in true hay fever.

The treatment of patients suffering from pseudo-hay fever consists in the removal of septic foci in the nose or the throat, the use of sprays and of vaccines prepared from organisms growing in the irritable mucous membrane, the removal of animals to which the patient is sensitized or desensitization to these animals' epidermal proteins and in the case of food sensitization, the removal of the offending food from the diet.

Asthma.

Ideas as to the ætiology of asthma have undergone a great change during the last ten years. The neurogenic and metabolic theories have gradually been replaced, at least in part, by the anaphylactic conception of asthma. It is possible that some cases of asthma have a neurogenic or metabolic basis, but it is difficult to be certain of such a diagnosis. In the protein sensitized patients, the protein may be of animal or vegetable origin, for example, from animal dandruff, foods, pollens and possibly bacteria.

The method of determining the cause of asthma is by the scratch or intra-dermal tests. The mode of preparing these testing agents may now be very briefly summarized. It is quite impossible to discuss full details of such method in this paper.

Preparation of Material for Cutaneous Tests.

1. *Animal Dandruff and Hair.*—The material is extracted with 14% alcohol or preferably with normal saline solution containing 0.35% trieresol and then filtered through a Pasteur-Chamberland filter. Both of these preparations have given similar positive cutaneous tests on the same patient.

2. *Food.*—Food rich in protein, such as lean mutton, beef, fish, egg white, are simply desiccated at low temperature. Caseinogen in milk is precipitated with weak acetic acid and the fat removed from the precipitate by ether.

The filtrate derived from the milk treated as just mentioned is used for the preparation of lactalbumin which can be precipitated by saturation with ammonium sulphate.

Vegetables and fruits are extracted with water for forty-eight hours, toluol being used to prevent bacterial growth; the fluid extract is then concentrated *in vacuo* at a temperature not exceeding 45° C. (Wodehouse).

3. *Pollens.*—Pollens of flowers, weeds and grasses are collected, thoroughly dried in a desiccator and then used as a powder for the scratch test or as solutions for the intra-dermal tests.

4. *Bacteria.*—These are prepared according to the method suggested by Chandler Walker. The bacteria are grown on agar for forty-eight hours. They are removed with normal saline solution, treated with alcohol, acidified with 0.5% carbolic acid, then with ether and finally dried (7).

The solutions for therapeutic injections are made as follows:—

1. *Animal Dandruff.*—A quantity of the material is soaked in one-hundredth normal sodium hydrate for forty-eight hours. The extract is filtered and the alkali-metaprotein in the filtrate is precipitated by neutralization with one hundredth normal hydrochloric acid.

This precipitate is separated by centrifuging and washed and a weighed quantity is dissolved in one hundredth normal sodium hydrate and preserved with trieresol. This constitutes the alkali-metaprotein. The various strengths are made by diluting with one hundredth normal sodium hydrate.

2. *Pollen Extracts.*—These are prepared by extracting a known weight of pollen with twenty times its weight of normal saline solution for forty-eight hours. The extract is then filtered through a Pasteur-Chamberland filter and trieresol added to make a 0.35% solution. The 1 in 20 extract is then diluted with sterile saline solution containing 0.35% trieresol so as to make the dilutions 1 in 200, 1 in 2,000 and 1 in 20,000. It is then ready for use. Recently Coca has advocated the use of an aqueous solution of sodium chloride, sodium bicarbonate and carbolic acid as the extracting agent for dandruffs, foods and pollens. The strength of the extract is determined by estimating its nitrogen content by the Kjeldahl method. These extracts are used for the intradermal tests and for the therapeutic injections.

Diagnosis of the Cause of Asthma.

An attempt must be made to distinguish between asthma

and asthmatic bronchitis. The cutaneous tests either by the scratch or intradermal method are the only means of determining the exact nature of protein sensitization, but these tests are by no means infallible and a large percentage of "negative" results is obtained.

Treatment of Asthma.

Where positive responses to the cutaneous tests have been obtained, the treatment varies with the nature of the test.

If the offending protein is contained in food, then the food is usually eliminated from the diet. If animal dandruff is the causative factor, the animal may be removed from the immediate environment or in some cases desensitization is attempted. In pollen sensitized persons desensitization should be performed.

In patients who do not react to the cutaneous tests, non-specific measures have to be adopted. The taking of simple meals with avoidance of supper and treatment of constipation are important. Peptone injections have been reported by some as being useful and non-specific autogenous vaccines are frequently of value. Adrenalin or atropine and morphine are valuable for alleviation of acute symptoms and a mixture of potassium iodide, tincture of stramonium and *liquor arsenicalis* given over a long period is perhaps the best medicinal treatment for chronic cases.

Operative removal of septic foci especially in the nose and throat and attention to nasal abnormalities are frequently necessary.

It is probable that further research will disclose that a much larger percentage of asthmatics suffer from protein hypersensitiveness and will reveal the specific causative factor. If such an ideal is attained, the prospect of effective therapeutics in this distressing malady should be much brighter.

Results.

I have referred in previous communications to the detailed results obtained in true hay fever and asthma. The following figures apply to three hundred and one patients suffering from either true hay fever, pseudo-hay fever or asthma or any combination of these.

TABLE II.

Affection	No. of patients	Ps'tve cutaneous reactions	Number of pat'nts treated by specific measures	Completely or almost completely relieved	Partially relieved	Not relieved
True Hay Fever	130	119	74	74.3%	21.6%	4.1%
Pseudo-Hay Fever	35	5	3	0	All	0
Asthma	136	60	42	59.5%	28.6%	11.9%
Total	301	184	119	—	—	—

A considerable number of patients who reacted to the cutaneous tests, are not included in the above list of therapeutic results as their treatment had not proceeded far enough to judge of its efficacy. This list does not contain the results of treatment of patients who failed to react to the cutaneous tests.

Owing to the compilation being made at the close of winter, a large number of winter asthmatics and pseudo-hay fever patients are included in the list; these lower the percentage of positive cutaneous reactions which are always much more numerous in the spring and summer months.

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(4) Wodehouse, *Boston Medical and Surgical Journal*, March 29, 1917, page 85.
(5) L. A. I. Maxwell, THE MEDICAL JOURNAL OF AUSTRALIA, June 23, 1923, page 693.
(6) H. H. Dale, *Journal of Pharmacology and Experimental Therapeutics*, 1912, Volume IV., page 167.
(7) I. C. Walker, "Asthma; Hay Fever," Oxford Medicine, 19.

PROFESSOR W. CARMALT JONES said that Dr. Maxwell had accepted Dale's hypothesis of anaphylaxis, namely that the antibodies due to the sensitizing dose were lodged in the cells and that the exciting dose led to a reaction comparable to a precipitin reaction in the cell bodies with consequent classical disturbance. This was interesting in another connexion. Dale had suggested that cells and tissues depended for their identity on their proteins and that the cells resented the introduction of the foreign protein by action of this kind. Perhaps the infertility of hybrids depended on this phenomenon.

He found that hay fever was not as successfully treated with stock pollen extracts in New Zealand as in England. He thought that this was due to some differences in the prevalent pollens. At the same time it made it necessary to seek for other methods of treatment. Auld had introduced the use of peptone as a non-specific densensitizer. The common sense of his method was that if an animal were sensitized to several proteins, such as milk, horse serum and egg albumin, and then desensitized to one, for example, milk, it would be found that it had been desensitized to all. Auld had suggested the use of peptone in immunizing doses because peptone produced asthma in animals. Peptone might be used quite successfully in the treatment of certain forms of asthma. Auld had gone beyond this and had suggested its use in other spasmodic conditions, including epilepsy, migraine and even Menière's disease. Professor Jones had treated a young girl who had had epileptic fits at every menstrual period. This had seemed to him clearly the kind of condition likely to be due to protein disturbance. After a course of peptone this patient had been free from fits for at least a year and no recurrence had been recorded.

There were other aspects in asthma besides protein sensitiveness. An irritable respiratory centre could not be left out of consideration. The common phenomenon of sneezing when a person looked at the sun indicated by what indirect paths the centre might be reached. The functional nervous element was familiar. A hay fever subject might be precipitated into a paroxysm by the sight of a cinematograph film of a waving field of hay. For successful treatment all sources of peripheral irritation of mucous surfaces should be removed in susceptible patients. He had records of patients who had not been relieved until polypi in the nose, septic teeth and a tapeworm had been removed. The use of bromides was of definite value; they acted as sedatives to the irritable centre.

CIRCUS MOVEMENT IN THE AURICLE IN AURICULAR FLUTTER AND FIBRIELATION.

By W. N. Horsfall, M.B., B.S. (Melbourne), *Sydney.*

It will perhaps be of advantage to refer to the mechanism of conduction in the auricle beating normally and to indicate some methods by which this information has been obtained.

If we take a simple strip of muscle (see Figure I.) and place the two ends in circuit with a galvanometer and then stimulate one end *P*, we find a movement in the galvanometer showing two deflections, one upwards and the other downwards. The first upward deflection is due to the activity of the muscle at *P*. When muscle passes into activity, it becomes relatively negative or "*Z*incative" to inactive muscle. As *D* becomes active, it is relatively negative to *P* and we get downward deflection. When both

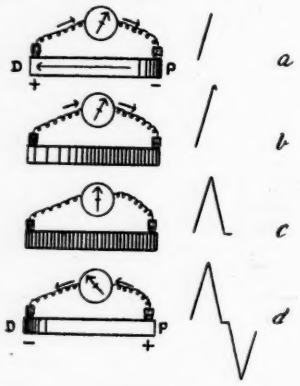

Figure I.

A Diagram Illustrating the Progress of an Excitation wave along a strip of muscle from P to D. The corresponding movements of the galvanometer string are shown to the right (after Lewis).

ends are equally active, the string is stationary, as the muscle is iso-electric.

If we stimulate our strip of muscle at *D*, the resultant curve is reversed. It is reversed because *D* is at first negative to *P* and the first deflection is a downward one, because the current flows through the galvanometer in the opposite direction. By the application of this principle we can tell the direction in which a wave is travelling in the dog's auricle. We place two non-polarizable electrodes on a dog's auricle and wires lead off from each to a string galvanometer. We name these electrodes *Z* and *C*. respectively.

If in a broad sheet of muscle (see Figure II.) the wave travels from *A* to *B*, the first movement of the string or initial deflection is upward as *Z* becomes first negative to *C*. If the wave travels from *B* to *A*, it is downward; if from *X*, the movement of the string is broken up and shows no initial deflection. According to the movement of the string upwards or downwards we know the direction of the wave.

In this way the course of the wave in the dog's auricle has been mapped out. It is not only the direction of the wave that can be determined from the deflection observed. The time the wave takes to get to any particular part of the auricles can be found out by taking a record from a limb lead simultaneously with a direct record from the surface of the dog's auricle, both recording on the same photographic plate. The limb lead record does not vary. It is constant from one plate to another. We can time

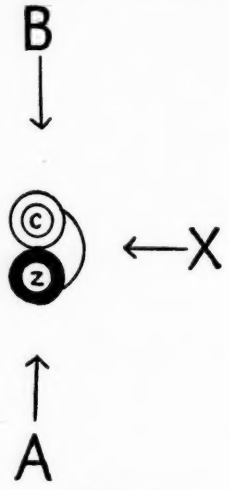

Figure II.

the arrival of the excitation wave at a definite point in the auricle relative to the apex of the *P* wave in a limb lead. Similarly we can time the arrival of the wave at every point in the auricle relative to the apex of the *P* wave. Consequently we can time the arrival of the wave at each

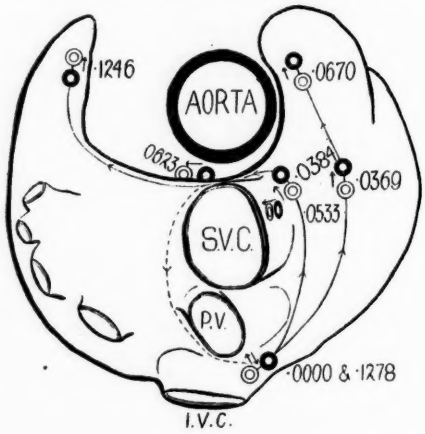

Figure III.

An Outline of the Dog's Right and Left Auricle whilst normal rhythm was in progress. Indicated thereon are the times of the arrival of the excitation wave at different surface points, the reading from the base of the superior vena cava being considered as zero. The arrows indicate the path of the wave as judged by the direction of the deflections (after Lewis).

point in the auricle relative to every other point. Thus it is found in one experiment that the wave appeared under our contacts on the sino-auricular node 0.0038 second before the summit of *P* in the limb lead. When another record was taken and the contacts were placed on the inferior *vena cava*, the wave passed the inferior

vena cava contacts 0.0221 second after *P*. Therefore the wave took 0.0259 seconds to travel from the sino-auricular node to the inferior *vena cava*.

In this way it has been proved that the earliest point in the auricle to become active is in the region of the sino-auricular node. The wave spreads down the tænia. In the heart beating normally the excitation wave has reached all parts of the auricle virtually while the upstroke of the peak *P* of a limb lead is inscribed or very soon afterwards. Figure III. shows the spread of the wave and the time of the arrival of the wave at different surface points of the auricle during normal rhythm. If the dog's heart was beating one hundred and twenty times

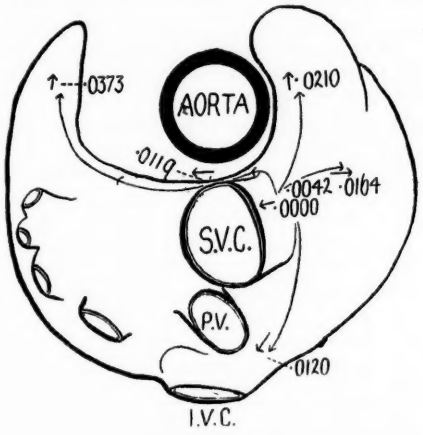

FIGURE IV.

An Outline of the Dog's Right and Left Auricle whilst flutter was in progress. Indicated thereon are the times of the arrival of the excitation wave at different surface points, the reading from the base of the inferior vena cava being considered as zero. Each of the readings has been determined relative to the apex of P in a limb lead and can therefore be determined relatively to each other.

per minute, there would be an interval of 0.5 second between two successive waves at any given point in the auricle.

Circus Movement.

Auricular flutter is a simpler condition than auricular fibrillation. The two have many points of resemblance. The evidence for circus movement in fibrillation is led up to by the work done in flutter. We can now refer to the investigation of flutter.

In the dog it is possible to produce auricular flutter. If we stimulate the auricle of a dog's heeart by weak faradic stimulation that is stimulation at a rate of two or three thousand stimuli per minute or by rhythmic stimulation at about four hundred per minute, then on the withdrawal of the stimulation a certain after-effect is sometimes seen which lasts for a variable period. This after-effect may be auricular flutter, impure flutter or fibrillation on different occasions.

When a condition of flutter is established, we examine the surface of the auricular muscle precisely as we examined the auricular muscle when the normal rhythm was in progress.

Leads are taken from different parts of the auricle at the same time as a limb lead is recorded. We time the arrival of the wave at various points on the auricle.

Figure IV. shows an outline of a dog's auricle and indicated thereon is the spread of the wave. Over a series of experiments the time of arrival of the wave at our different contacts has been determined and the direction of the wave also as shown by the small arrow alongside each pair of contacts. The times are marked relative to the arrival of the wave at the inferior *vena cava* contacts represented as zero. That is to say if the wave appears at the inferior *vena cava* at 0.0885 second before the summit of *P* in one limb lead and on the tip of the right appendix 0.0215 second before the summit of *P*, then the reading at the latter point relative to the reading at the inferior *vena cava* as zero is 0.0670 second. Figures III. and IV. were taken during the same experiment with normal rhythm and flutter respectively. The wave passes the inferior *vena cava* contacts 0.0885 second before the apex of *P* and again 0.0393 second after the apex of *P*, making a cycle of 0.1278 seconds.

Looking at our diagram we see that the wave was travelling from the inferior *vena cava* up the tænia. Normally it travels down the tænia. It went from right to left across a band of fibres joining the two auricles above the superior *vena cava* to the tip of the left auricular appendix. The whole auricular cycle lasted 0.1278 second

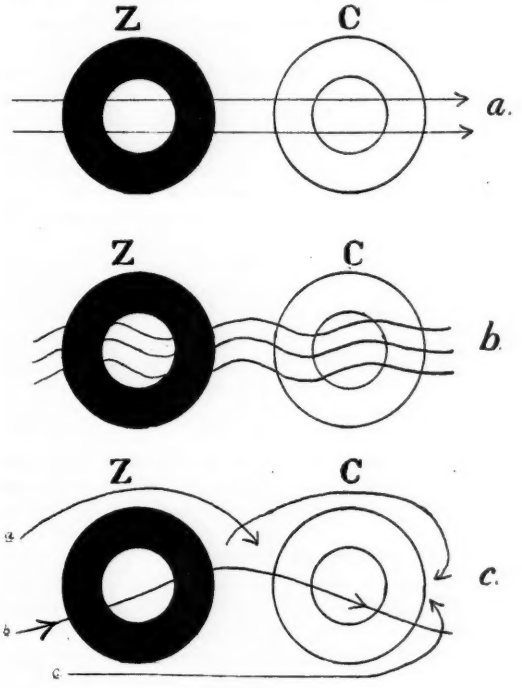

FIGURE V.

Representation of Wave under Two Contacts on the Auricular surface. a equals normal rhythm; b equals flutter; c equals fibrillation. Three waves are shown.

and as the wave is found at the tip of the left appendix in 0.1246 second, some part of the auricle is becoming active during the whole period of the cycle. There is no true diastole. It will be remembered that in the heart beating with a normal rhythm the wave has spread almost over the whole auricular surface, whilst the upstroke of

P is inscribed from a limb lead. There is thus an interval of 0.1278 second between two successive waves at any given point in the auricle.

Compare the time taken for a wave to travel from the sino-auricular node region to the left appendix while the heart is beating normally (see Figure III.) namely 0.0373 seconds, and the time taken during the period of flutter over the same distance, namely 0.0862 second. We find the rate of transmission of the wave is much reduced in flutter. In the normal heart it travels about one thousand millimetres per second; in flutter about five hundred millimetres per second.

Now the theory is and there are many more facts to prove it that in this experiment the wave was travelling from the region of the inferior *vena cava* up the tænia, round the corner of the superior *vena cava*, to the left of the superior *vena cava* and back again to the region of the inferior *vena cava* 0.1278 second later. Arrived there the wave repeats its path and begins another cycle. The movement can be likened to a dog turning in a circle and trying to catch his own tail. If he catches his tail the movement stops. The interval between the head and tail corresponds to the gap of tissue which is not refractory or tissue which has recovered from its refractory state and can therefore conduct an impulse. It is a small gap and can be measured. It is about one-fiftieth of a second or ten millimetres long.

Knowing the rate of the wave in flutter and the distance a circular wave would have to travel along our circular path from the inferior *vena cava* and back to inferior *vena cava* which is about sixty-seven millimetres, we can calculate the time of the arrival of the wave at the inferior *vena cava* from one cycle to the next. The calculated period corresponds to the period experimentally determined within a small margin of error.

In flutter then a wave is circulating round the superior *vena cava* opening. It may not always course round this opening. It may course round any other natural opening in the auricle, such as the auriculo-ventricular opening. In the case investigated it went in an anti-clockwise direction. It may revolve in a clockwise direction.

We must recognize a central circulating path and centrifugal waves sent as offshoots from this central path which spread over the whole surface of the auricles during each cycle and not as in normal rhythm during one small part of the cycle, namely during the period covered by the upstroke of *P*.

Auricular Fibrillation.

In fibrillation the evidence of a circus movement is more involved, but it is clear and definite. In flutter the wave proceeds with regularity from cycle to cycle, both the central wave and the centrifugal waves in outlying parts of the auricle.

The auriculo-ventricular node is consequently excited at regular intervals and the response of the ventricles is regular. The response of the ventricles is regular, but not at the same rate as the auricles. The auriculo-ventricular node cannot transmit impulses at this fast rate, say of three hundred per minute. It transmits at one half or one quarter the rate in which case the ventricles beat regularly at one hundred and fifty or seventy-five per minute, a condition of 2:1 or 4:1 flutter. We may have a mixture of both, in which case the ventricular response is irregular.

The essential features of auricular fibrillation are: (i.) The rate of the auricular oscillations is quicker, being about four hundred and fifty per minute in man. The oscillations are quicker because the diameter of the circle is smaller and the waves can complete a circus movement more quickly. I wish here to emphasize the distinction between the rate of the oscillations, that is the number of cycles completed per minute, and the speed at which the wave travels. As pointed out previously the speed of the wave is slower by about one half than the speed of the normal wave.

(ii.) The regularity of either the central wave or the centrifugal waves from cycle to cycle is not maintained as it is in flutter. The wave is broken up by barriers of tissue which are refractory. An electro-cardiographic record taken with direct leads from the auricle or a limb lead shows no uniformity from cycle to cycle. The deflections of a direct lead may be upwards or downwards or split up. The wave is not travelling with uniformity under our contacts. Some waves are delayed and some get lost in a maze of muscle fibres which are in a refractory condition and have not recovered from their previous contraction. Hence it is that the response of the ventricles is irregular, irregular because the waves reach the auriculo-ventricular node at irregular intervals. Just as many waves pass down the bundles as the node can pass.

In flutter we conceive of the passage of the wave through fibres some of which are refractory. The course is finely sinuous and of a degree which causes no alteration in the appearance of the galvanometric curves as obtained by direct leads from cycle to cycle. The impediment is microscopical. This impediment delays the rate of transmission of the waves.

In fibrillation the impediment is gross. The course of the wave is deflected to such an extent as to become macroscopical. The appearance of the galvanometric curves are distorted from one cycle to the next.

In Figure V. *a* representing the normal rhythm the wave is represented as travelling in a straight path under our contacts. In flutter (Figure V.) *b* the wave is shown as bent by passing through fibres which are refractory. In fibrillation the wave may be split. It hits our contacts at varying angles and because it pursues this changing path, it reaches outlying parts of the auricles at varying time intervals from cycle to cycle. We know that the wave hits at varying angles, because our deflections vary from cycle to cycle when we place contacts on the surface of the auricle. Some deflections are delayed in point of time; others are directed upwards or downwards in different cycles.

An appreciation of these points throws light on the ventricular activity as seen clinically in auricular fibrillation.

In the compilation of this paper I have referred freely if not entirely to the works of Sir Thomas Lewis and his co-workers, to the Journal of *Heart*, Volumes VII. and VIII., to Lewis' "Mechanism and Graphic Registration of the Heart Beat" and to the Philosophical Transactions of the Royal Society (1914) Volume CCV., *B.*, pages 375 to 420.

DIGITALIS AND QUINIDINE IN AURICULAR FIBRILLATION.

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Digitalis and quinidine are used from an entirely different point of view; they cannot replace one another, though digitalis may often make the use of quinidine possible in severer grades of heart failure.

Digitalis owes its reputation to heart failure in association with fibrillation and is not nearly so potent with normal rhythm, especially in toxic types. Digitalis exerts two principal effects: (i.) an indirect action increasing vagal inhibition, (ii.) a direct action on the conduction system.

The writer pointed this out in 1911 (1) using atropine to abolish vagal inhibition before and after digitalization. Lewis and co-workers (2) re-examined the question using the cardiograph and larger doses of atropine and found the same results.

There can be little doubt that, owing to the brilliant researches of Lewis and his collaborators (2), circus movement is the mechanism producing auricular fibrillation.

The number of oscillations in the auricle is very high, something over four hundred per minute. At any given moment excitation waves traversing the auricular fibres find some fibres responsive and conduct the stimuli; some are refractory and block the stimulus; some are partially refractory and hinder or delay the passage of the stimulus. The consequence is that the stimuli arrive at the auriculo-ventricular node at irregular times. A certain number only can traverse the conduction fibres and the ventricle response is irregular and more or less rapid.

Now the direct action of digitalis on heart muscle and especially on the conduction system is here manifested to advantage. Incidentally it seems likely that part of this effect is brought about by prolonging the refractory period of the auriculo-ventricular node (3). By damping down the function of conduction less stimuli traverse the junctional tissues and therefore the ventricle is driven less rapidly. The degree of block depends on the dosage. Slowing the ventricle removes the exhaustion factor, for it is the "pace that kills" not the irregularity. In addition the ventricle has more time to be filled with blood and therefore delivers it in more uniform amounts. Whereas, before digitalis, the ventricle beats are constantly varying in force and frequency, big beats and little beats, short pauses and long pauses are all mixed up indiscriminately, now the feebler beats drop out and are replaced by a series of beats still irregular, but much more uniform. It is important to show that digitalis does not affect the fibrillation process in the auricle as such, indeed it may be accelerated; it protects the ventricle and the pump is better filled and delivers blood in more even output.

This point needs emphasis, because the pulse may approach regularity and the fibrillation thought to be ended, but remove the drug and the rate progressively rises and becomes again as irregular as before with the same degree of heart failure. Or, if exertion or emotion quickens the rate, the irregularity is again obvious.

Spontaneous recovery from long continued auricular fibrillation has been seen by the writer in two patients, one while under digitalis, one without, but such cessation is the exception.

The digitalis effect of slowing the ventricle and thus allowing of improved power and tone of the muscle exerts a favourable effect in many directions. The coronary arteries are better filled and the nutrition of the heart muscle thereby improved. The general circulation is improved and allows of tissue recovery, the most striking feature being the relief of dyspnœa; the renal pressure is improved and the kidneys secrete better. Digitalis is not a direct diuretic; dropsical effusions are run off and the patient regains more or less reserve. The importance of maintaining the digitalis effect will be discussed later.

In normal rhythm the indirect effect of digitalis on the vagus is to cause sinus slowing and a fall in rate of only a few beats per minute. The direct effect on the conduction tissues may cause partial heart block and a few ventricular responses may drop out. There is nothing in such fall of rate to compare with the decrease in cases of auricular fibrillation which may often slow the ventricle from one hundred and thirty or one hundred and forty per minute to seventy or less, according to dosage. For the acute stage when symptoms of distress are evident, the drug must be pushed to get the greatest benefit.

To play with 0.3 mil (five minim) doses of the tincture is to use a valuable remedy as an indifferent bitter and yet such practice is not uncommon. The tincture is a reliable preparation and greatly to be preferred to the infusion. It should be emphasized that the glucosidal principles are rapidly destroyed by hydrolysis, which is the reason why the infusion should be fresh and a good reason for not relying on it at all. Also, the tincture in water rapidly deteriorates so that the last doses of 240 cubic centimetre (eight ounce) bottle may be inert. The simplest method is to prescribe the tincture as such, so many drops to be measured out as required and freely diluted with water before swallowing or it may be combined with other flavouring tinctures.

In the stage of acute heart failure in auricular fibrillation one may use 1.2 mils (twenty minims) every two hours for six to twelve doses, then reduce to every six or eight hours and so on. The pulse rate or better still the heart rate should be carefully observed.

Some American workers, in particular Ward, Robinson and Pardee (4) base dosage on the amount of digitalis required to produce its physiological effects in proportion to the weight of the body. Pardee estimates two minims for each pound of body weight, that is a man weighing sixty-five kilograms would be given 14.5 to 18 mils. For safety half this amount per day is advised. Carey Coombs (5) advocates in severer cases of heart failure in auricular fibrillation one drachm (3.5 mils) doses every four hours for a day followed by half drachm doses for two or six days. The important point to notice is that large doses are necessary in acute failure and the physician should not be content with the maximum 0.9 mil (fifteen minim) dose of the Pharmacopœia.

Other signs of limits of tolerance for digitalis are vomit-

ing or nausea; also headache usually of a throbbing character. The vomiting is a central effect and not due to stomach irritation, though this may be so in part.

Another important sign for which watch should be kept when digitalis is used in auricular fibrillation, is the production of coupled beats. This is a rhythm in which each normal ventricle contraction is followed by extra-systolic response. The phenomenon is readily recognized by auscultation.

The second beat of the couple is an extra-systole and as far as my electro-cardiographic records show, it arises in the left ventricle. It is a danger signal of over dosago, causing irritation of the ventricle. Persistence with the drug after this stage may produce a fatality by inducing ventricle fibrillation. After the acute stage of heart failure is passed, digitalis can be reduced and a dose just sufficient to keep the pulse rate sixty to eighty aimed at. This may require quite small or infrequent doses after the preliminary thorough digitalization. The patients must also be made to realize that digitalis must be taken for the remainder of their life. If the drug is wholly withdrawn, the pulse rate progressively rises and becomes more and more irregular with concurrent return of heart failure. It is remarkable how long patients can be kept going on digitalis therapy.

Let us now consider the newer phase of fibrillation treatment, which is a direct attack on the auricle turmoil, and an attempt to restore it to normal action by the use of quinidine. Whatever view one takes of the advisability of its use, surely it is a brilliant triumph of therapeutics that such effect can be achieved.

The circus movement theory of auricular fibrillation must be understood to follow the rationale of quinidine action; in the experiment animal fibrillation is produced by "Faradizing" an auricle at very high speeds. In a proportion of instances, if the stimulation be withdrawn, fibrillation persists for a time. By timing the appearance of the excitation wave at different points of the auricle by electrodes leading to electro-cardiographs, the arrival of the excitation wave can be signalled and the path thus ascertained.

Again, if a ring of muscle from a heart be stimulated, the stimulus spreads in both directions equally. If rapid stimulation be sent in, they follow each other as fast as the muscle recovers from the refractory state. If the rapid stimulation be withdrawn, it may happen that the wave, spreading in both directions, meets a refractory barrier, let us say on the right side, but is free to travel round in the other direction. The oncoming wave now travels clockwise.

By the time the crest of the wave sinuously spreading through the interlacing fibres reaches the refractory barrier, this has passed off, so that the wave is free to traverse these fibres and so the circus movement becomes established—a never ending pursuit by the crest of the excitation wave chasing its own tail, like the head and tail of a comet. It never quite catches up. Now this gap is all important. Close the gap and the wave movement ceases. Prolong it and thus alter the time relations, the crest reaches a refractory barrier which brings it to an end. It is therefore obvious that drugs with the power of affecting the refractory period in the auricle, will prove the ones to divert the auricle from its disorderly ways into its usual sedate and orderly action.

So far quinidine sulphate is the best we know. It is five to ten times as powerful as quinine. Grant and Iliescu (6) find it is better than cinchonidine, cinchonine and quinine in order of potency named.

The creditable feature of quinidine is its power of influencing the refractory period in the auricle; unfortunately its action is not so simple nor invariable. Hearts differ and in some the refractory phase is the more evident, in others less desirable features appear.

The epoch making work of Lewis and his collaborators (7), (8), (9) has established that in auricular fibrillation: (i.) vagal stimulation quickens the auricle and slows the ventricle, (ii.) atropine slows the auricle and quickens the ventricle, (iii.) digitalis slows the ventricle and quickens the auricle, though not invariably.

Taking quinidine action in more detail, it invariably slows the auricle oscillations and decreases them progressively from over four hundred per minute to about two hundred per minute or less. This has two interesting side effects. The power of the conduction or junctional tissues (auriculo-ventricular node and the bundle of His) to conduct stimuli is naturally limited.

It, too, has a refractory period from which it must recover before the next stimuli can pass. In fibrillation hundreds of stimuli are knocking at the auriculo-ventricular door at all sorts of times and demanding passage. In the jostling a number get through in no special order and the ventricle beats irregularly. Slowing the auricle oscillations means that fewer stimuli reach the auriculo-ventricular node per minute. This means less tax on the conduction function and thus relatively more get through. Therefore in the preliminary stage of quindine treatment the ventricle rate rises.

This is important in practice because the added rise of ventricle rate not only causes unpleasant palpitation and distress, but may embarrass the ventricle so much that the ventricle fibrillates. If it does, there is no propulsion of blood and death ensues. It is advisable to slow the ventricle with a preliminary course of digitalis. A further result of the slowing of the auricle oscillations is that the circus movement may be slowed to the stage of auricular flutter, for example, at a speed of two hundred and fifty per minute. It exceptionally happens that the bundle of His conducts all these stimuli and thus brings about ventricular flutter. The output from the weak rapid ventricle action may produce such low blood pressure that severe, even fatal syncope may result. Fortunately this is exceptional.

Quinidine lengthens the absolute refractory period in the auricular muscle and in this way closes the gap between the crest of the circulating wave and its wake and thus the circus movement is brought to an end. This is the master action in stopping auricular fibrillation and its justification for clinical use.

Slowing the conduction time in the auricle allows more time for the refractory period to pass off and therefore permits re-entry of the circulating wave. It thus perpetuates fibrillation and explains why only about 60% of patients give a successful response.

In regard to the disadvantages of quinidine, it leaves the pathological changes which cause fibrillation, untouched.

Moreover, it is readily seen that relapses to fibrillation are common. The greatest danger results from its beneficial effect on stopping the fibrillation. This seeming paradox is readily understood when one thinks of the state of the auricle. For months, may be years, it has not contracted, merely flickering fibrillary movements traverse the fibres; opportunity for thrombus formation is thus obvious. When the normal contractions return in response to the normal stimuli from the sino-auricular node, such thrombus may be detached and swept into the circulation as an embolus.

This is a real danger, but in what percentage is uncertain. The most favourable cases to treat are those with recent onset of fibrillation before thrombi form.

Apart from these risks minor unpleasant symptoms frequently occur; severe headache is common, also vomiting and at times diarrhoea.

In regard to dosage the majority of my patients have been given 0.2 to 0.4 gramme (three to six grains) every four hours till normal. The majority respond in some three or four days or less, if they are going to. Some only needed seven doses. In several resistant cases I have been successful with five doses given at two hourly intervals.

One of my patients—Case 5 (10) with tendency to relapse, needed no less than four courses within three weeks; but he was then kept normal for eight months on three doses a day, so that where reversion to fibrillation tends to occur, it seems better to give three doses per day for some weeks at least.

Theoretically digitalis treatment would seem to render success with quinidine less likely, but this has not been my experience. It is essential to use a preliminary course of digitalis if there is much distress from heart failure or if the pulse rate is too rapid. One can then not only bring the patient into safer position for quinidine treatment and protect the ventricle from too great an increase in rate, but one can better estimate the reserve of the heart. It is not advisable to use quinidine with limited cardiac reserve and severe signs of failure, though one should give the patient the benefit of the doubt.

In the majority of cases successfully treated the subjective relief is most gratifying.

It cannot be emphasized too strongly that quinidine should not be used in the stage of severe heart failure or in very grossly damaged hearts.

Discrimination must be employed lest a valuable drug be brought into disrepute. Digitalis has been used since the days of Wuthering for a hundred and fifty years and will continue to be our chief cardiac ally. Quinidine has been introduced only in the last five years; obviously it is as yet on its trial and it is too soon to estimate its value with accuracy. However, the dramatic result of restoring normal rhythm in auricular fibrillation by quinidine is a great therapeutic triumph.

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(9) A. N. Drury and C. C. Iliescu, *The British Medical Journal*, October 1, 1921, page 511.
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DR. HAROLD RITCHIE agreed that quinidine was a very useful drug in arresting auricular fibrillation, but its use was most advantageous in the rheumatic type of auricular fibrillation in young subjects whose heart muscle was reasonably sound. In the anterio-sclerotic type the prospect of success was less and the risk of death was greater. These patients ran a special risk of embolism, especially if their cardiac lesion was of long standing. Quinidine should not be administered in the presence of severe heart failure. In these circumstances the administration of digitalis would often suffice to prepare the heart for the exhibition of quinidine.

DR. W. MARSHALL MACDONALD referred to the use of ouabain, a glucoside obtained from a plant of the same natural order as strophanthus, which he had employed with good results in the treatment of patients suffering from auricular fibrillation. He did not consider that those suffering from auricular fibrillation with a low pulse rate required treatment other than comparative rest. He mentioned the history of a patient who had gone through a strenuous course of military service. He had also seen patients in whom fibrillation had ceased spontaneously and in whom cardiac dilatation and liver enlargement had very considerably diminished twenty-four hours after the pulse had become regular.

DR. SILBERBERG in his reply to Dr. Ritchie said that he did not agree that patients with arterio-sclerotic degeneration should not be treated with quinidine. He quoted the records of three patients, aged seventy-five, sixty-eight and sixty-four years respectively. He agreed that digitalis should be given first to produce better compensation. Dr. Blackburn and Dr. Macdonald had mentioned that pace alone did not kill. Against this it could be said that auricular fibrillation implied degeneration and that the added factor of speed exhausted the ventricle. He had not used ouabain, but had found strophanthin very valuable at times when given intravenously. He had seen spontaneous arrest and of paroxysmal fibrillation in patients whom he had treated with quinidine. He thought that the duration of the attack had been materially shortened.

DR. W. N. HORSFALL in discussing Dr. Silberberg's paper said that the action of digitalis was the establishment of a degree of block in the auriculo-ventricular node. Digitalis should be considered to be a poison with a specific action on the primitive tissue of which the node consisted. The node was part of the remains of the primitive cardiac tube of man's invertebrate ancestors. When digitalis was given in full doses, the well known coupling of the heart beats or bigeminal pulse was produced. The second beat of the couple was an extra-systole arising in the ventricle. If the heart rate was sixty to the minute and the heart exhibited coupling under the influence of digitalis, there would be only thirty impulses in each minute transmitted from the auricles to the ventricles. Such a condition would approach a complete block between the auricles and the ventricles. The action of digi-

talis was to delay the conduction through the node. This was effected by poisoning the nodal tissues and thus prolonging the refractory period of the node. When coupling arose, the dose of digitalis should be lessened or the drug should be stopped for a short time. Dr. Horsfall maintained that digitalis medication did not raise blood pressure as was generally supposed. This might sound like heresy. He stated that it did not increase the diastolic period, nor did it slow the heart rate when the heart was beating with a normal rhythm.

Quinidine was of very great value, but it should be used only in selected cases. It should not be given when the patient had had heart failure previously with congestion. He would not give quinidine to old people with long established auricular fibrillation. He would give it to young adults who had recently acquired a rhythm of auricular fibrillation and who had a healthy heart muscle. Between these two extremes there was room for the exercise of some judgement as to whether the drug should or should not be used.

In reply to the several speakers who had discussed his own paper on auricular fibrillation and auricular flutter, he said that they had had their attention rivetted on valvular lesions as a sufficient diagnosis of a cardiac affection for many years. More recently they had taken up the subject of the efficiency of the cardiac muscle. This view had been held one hundred years previously and was the correct view. There was a danger that they might be induced to regard a disturbance of rhythm, such as auricular fibrillation, as a diagnosis and of necessity a very serious condition. Some of his patients had told him that they were threatened with auricular fibrillation. He regarded that as a wrong attitude to take up. It was the efficiency of the cardiac muscle that had to be considered. When the rhythm was disturbed the heart was handicapped in its work. They could help the rhythm or change it, but they should always fix their attention on the quality of the cardiac muscle. They should recognize that it was not always desirable to attempt to change auricular fibrillation into a normal sino-auricular rhythm. For example in exophthalmic goitre when the pulse rate was regular and one hundred and forty per minute, they were powerless to control the rate. But if the pulse became suddenly irregular, they would know that auricular fibrillation had developed. Then they could control the ventricular rate with digitalis. If he could produce auricular fibrillation in such a condition, he would do it. He would not attempt to change the rhythm of fibrillation to a normal rhythm under these circumstances. He stated that the prognosis was better in a patient with heart failure with congestion in the presence of fibrillation than in a patient with the same condition and a normal rhythm. In the former they could control the ventricle, but in the latter they could not.

At times they saw patients with fibrillation with a ventricular rate of eighty per minute in a standing position. One patient, a surgeon, was able to do his work well, although he had had fibrillation for twelve years. He had left this patient alone. He would only convert him into a neuropath by interference. Of course the knowledge of his cardiac condition was of importance, should the patient become ill from some other cause. He held that the condition in these patients was an impure flutter rather than fibrillation. There were all grades between pure flutter and fibrillation. Auricular fibrillation was in essence a changed rhythm, but not a disease.

RENAL INSUFFICIENCY.

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In introducing the discussion on renal insufficiency Dr. Sinclair Gillies reviewed the physiology of the urinary secretion and its bearing on the hydræmic and azotæmic type of insufficiency. He continued as follows:

The work of recent years has thrown considerable light on renal insufficiency and compels us to reconsider our views on the subject of chronic interstitial nephritis.

Briefly the characteristics of chronic interstitial nephritis were said to be polyuria, albumin present in the urine in small amount, urinary chlorides normal, urea decreased in the urine, urea and purin bodies increased in the blood œdema absent, blood pressure raised, heart hypertrophied, a tendency to uræmia.

It has long been noted that though the above is the typical picture, numerous exception occur. At one end there is the patient with high blood pressure and hypertrophied heart with little or no evidence of renal involvement dying eventually of cerebral hæmorrhage or cardiac failure. At the other is the typical uræmic patient with normal pressure and no cardiac hypertrophy. Between these extremes every grade exists, forcing us to the conclusion that chronic nephritis is only part of a much more general cardio-vascular disease which, when the brunt falls on arterioles other than those of the kidneys, produces the condition described by Clifford Allbutt as hyperpiesis. When the renal vessels are mainly involved the typical picture of chronic nephritis results.

Geoffrey Evans in his Goulstonian lecture on the nature of arterio-sclerosis said: "My interpretation of the association of diffuse hypertrophic (vascular) sclerosis and chronic nephritis is that both lesions are produced by the same cause or causes and the solution of the ætiology of chronic nephritis will solve the ætiology of diffuse arterio-sclerosi."

In its production he considers inflammatory reaction to be of the first importance.

"Its development in its extent and form depends on a balance between the action of toxic agents and the power of resistance of the vessel wall to attack."

This conception of chronic renal disease, while correlating and explaining satisfactorily the varying types of chronic nephritis, raises the question how far the usually accepted symptoms of renal inefficiency depend on actual renal defect and how far they depend on concomitant vascular changes and failure of function in other organs.

The symptoms ascribed to uræmia in the latest edition Osler's text book are headache, mania, delusional insanity (*folie Brightique*) convulsions, general or local, uræmic amaurosis without fundal change, uræmic deafness, coma with or without convulsions, dull and apathetic condition with twitching, local palsies, itchiness, cramps, dyspnœa (continuous paroxysmal Cheyne-Stokes's breathing), vomiting, diarrhœa, foul tongue, stomatitis, anæmia, wasting. How many of these can be attributed with certainty exclusively to renal inadequacy? There is no doubt that

convulsions are frequent without demonstrable failure of renal function. They are met with in patients with high blood pressure, may recur at intervals and are compatible with many years of good health after their occurrence. Such cases may be explained possibly by vascular spasm or cerebral œdema resulting from the condition of the cerebral vessels, as too may the cases familiar to all, of recurring aphasia and localized paralyses. A similar explanation may be offered for many of the mental symptoms encountered chiefly in cases of chronic Bright's disease with high tension and failing heart. Still other of the above mentioned symptoms are capable of explanation by extra-renal causes, reducing further those symptoms attributable to renal defect alone. The ground for removing such cases from the category of uræmia is the fact that in them the accepted tests for renal efficiency detect no gross defect in renal function. On the other hand in view of our ignorance of the ultimate cause of uræmia this argument must be accepted with some reserve. In this connexion one recalls the absence of symptoms in patients dying after complete abolition of the renal function, as in the removal of the only functioning kidney. Enough has been said to show the need for revision of our views on this subject.

For a number of years workers all over the world have been endeavouring to evolve an adequate gauge for determining renal efficiency and many tests have enjoyed temporary popularity. None of them are satisfactory as indicators of slight defect, but taken together they are of much value in detecting gross deficiency, sometimes before its magnitude is suspected from observation of clinical symptoms.

The more important of these tests fall under the following headings:

Urea Content of the Blood.

The determination of the blood urea as showing whether the kidney is excreting urea satisfactorily.

Normally blood contains from fifteen to forty milligrammes of urea per hundred cubic centimetres. When the amount rises above forty milligrammes there is suspicion of some defect in the renal excretory power; increase above fifty milligrammes is definite evidence of such defect with the exception of some cardiac conditions and after severe vomiting and purging.

Unfortunately this test is of value only in advanced cases, as it has been shown experimentally that three-fourths of the kidney tissue can be removed before accumulation of urea appears in the blood.

Accompanying this increase there is generally a rise in the inorganic phosphates. Normally existing as three milligrammes per hundred cubic centimetres, they rise in acute nephritis five or even seven milligrammes. De Wesselow has shown that the presence of ten milligrammes or more is of the gravest significance; also that an increase in blood urea is of worse significance if accompanied by an increase in inorganic phosphates. His observations show a closer connexion between the onset of uræmia and the retention of phosphates than of urea.

Urea Concentration Factor.

The relation between the amount of urea in the blood and that secreted in the urine at the same time, known as the urea concentration factor, gives useful information regarding the functional activity of the kidney. Normally urine contains about seventy times as much urea per hundred cubic centimetres as does the blood. Progressive decrease in this proportion occurs in renal inefficiency. Where the factor falls below ten the outlook is serious. Ambard worked out a mathematical constant in this connexion, but its accuracy is open to question.

The urea concentration factor must not be confused with Maclean's urea concentration test, a simple and practical method of detecting advanced inefficiency. It is found that if fifteen grammes of urea be given in hundred cubic centimetres of water and the urine tested at the end of one and two hours the percentage of urea should exceed 2. If the urea content is above 2.5% the function is considered good.

The test is easily performed and is of undoubted value giving information before urea is found in excess in the blood. It is also a check on the blood urea test, as high blood urea with high urinary concentration has not the same bad prognosis as high blood urea with low concentration.

In the hands of the surgeon it has proved a valuable guide as to the safety or otherwise of operative interference. Unfortunately like the preceding test it does not necessarily give warning till extensive renal degeneration has taken place.

The phenol-sulphone-phthalein test of Rowntree and Geraghty is popular with our surgical *confrères* and is of undoubted value from their point of view. But like the urea tests it fails to detect the renal condition with function lying between a normal excretion, *id est* of 80% and 85% at the end of two hours and the moderately diseased kidneys with an excretion of 60% at the end of that time.

Increase in the blood content of uric acid and creatinin form the basis of less used tests for renal inefficiency.

The determination of the diastatic power of the urine gives information when considered in conjunction with other tests, but taken alone it is not always reliable.

Admitting that the above tests are of value only when renal inadequacy is fairly advanced, what earlier evidence have we of commencing renal disease?

Albuminuria from being considered of grave import, now runs the risk in some quarters of being shorn of any significance whatever. In this regard to my mind the pendulum is swinging over far. While albuminuria in adolescents or when accompanied by pus, spermatoza or other demonstrable local cause frequently is without significance of renal degeneration, yet its presence if accompanied by casts or raised blood pressure cannot be dismissed as of little importance simply because tests for gross disease show nothing. Remember that three-quarters of the kidney substance may be obliterated before these tests are definite and that the fact that a large number of soldiers showed albuminuria without other evidence of renal disease and were not more prone to war nephritis, an admittedly acute specific infection, is not proof that their kidneys were free from degenerative change. It only proves that they did not develope signs of gross renal inefficiency during the relatively short period they were under observation.

Again renal disease like disease elsewhere may be ar-

rested at any stage dependent on the cessation of the toxic cause, so that failure of a case of albuminuria to progress to a condition of typical renal disease does not necessarily exonerate the kidney. The position of casts in relation to renal disease is much that of albumin. While little weight need be placed on the presence of a few granular and hyaline casts, repeated presence of granular and cellular casts in moderate numbers probably means some grade of chronic nephritis.

One factor in the discounting of casts is probably the fact that the older observers examined the sediment of a urine that had stood for twenty-four hours, while the pathologist of to-day takes the more concentrated sediment of a centrifugalized specimen.

The significance of vascular and other changes in the retina in arterio-sclerosis and renal disease has recently been debated very fully at the Royal Society of Medicine.

The result of the discussion confirms the view that the changes found in cases of high arterial pressure and arterio-sclerosis differ in type and prognostic significance from those seen in typical chronic nephritis. It also supports the view that both types are due to a common cause.

Lack of time has permitted only a very cursory review of this large subject and has precluded any mention of treatment and prognosis.

To conclude I would emphasize the view that the changes occurring in the kidney in chronic renal disease are only part of a wide-spread reaction of the smaller vessels to the action of some unidentified toxin, that the symptoms referred to renal inefficiency are in part at least due to concomitant disease elsewhere, that our tests for inefficiency, though of value in moderately advanced cases, fail to detect slight and early changes, that valuable information is still to be got from the presence of albumin, casts and ocular changes, that we are still ignorant of the ultimate cause of uræmia.

I would suggest that in the discussion attention should be directed to the following points: (i.) The relationship between renal disease and the various symptoms grouped under the term uræmia; (ii.) the significance of the presence of albumin, casts, raised blood pressure and eye changes; (iii.) the value of the various efficiency tests and (iv.) the ultimate causes of renal degeneration and their prevention.

RENAL EFFICENCY TESTS: OBERSEVATIONS ON NON-PROTEIN NITROGEN.

By D. W. Carmalt Jones, M.D., F.R.C.P.,
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The opener has described the renal efficiency tests. I will confine my remarks to the one which the biological chemists at Dunedin regard as the most valuable single test. I should state at the outset that I am largely indebted here to Dr. C. S. Hicks, of Dunedin, now on his way home to take up a Beit fellowship, to whose great chemical attainments and personal enthusiasm the high standard of blood-chemistry now maintained at Dunedin is chiefly due.

I believe that the most valuable single test of renal function is the estimation of the non-protein nitrogen or the non-coagulable nitrogen. It depends on the complete precipitation of all the proteins by Folin's method and the estimation of the nitrogen of the urea, uric acid, creatin and creatinin and amino acids.

The method is briefly as follows: Two cubic centimetres of blood are withdrawn from a vein. Ten cubic centimetres are required if all the chemical constituents of the blood are to be investigated. The patient must have fasted for about twelve hours. The blood is commonly taken the first thing in the morning. The blood is placed in a test-tube containing ten milligrammes of potassium oxalate for ten cubic centimetres of blood and shaken to mix well with the oxalate.

It is then laked in seven volumes of water to one volume of blood. One volume of 10% sodium tungstate is added and then one volume of two-thirds normal sulphuric acid with continual agitation. The proteins fall down like so much mercury and leave a water-clear liquid. The non-protein nitrogen is then estimated by a modification of the Kjehldahl method.

The normal content of the blood of non-protein nitrogen is about thirty milligrammes per hundred cubic centimetres in hospital patients. However, without renal disease it is frequently as much as forty and only above this figure need anxiety arise.

In general the non-protein nitrogen is about double the urea nitrogen and may generally be taken as such, except during pregnancy where the figures may be as five is to one.

In acute nephritis the non-protein nitrogen is much increased and varies much from day to day. Repeated examinations are therefore required and constitute a valuable indication of recovery and of the efficiency of treatment. A young man was brought in recovering from an acute uræmic fit. His non-protein nitrogen was one hundred and thirty milligrammes per hundred cubic centimetres. A week later it was one hundred and two weeks later normal; he left the hospital recovered.

Increased non-protein nitrogen is of great value in the diagnosis of uræmia. Recently a woman was brought into hospital comatose and without a satisfactory clue to her condition. Her urine was of normal specific gravity and contained no albumin. Her non-protein nitrogen was one hundred and forty. She died and showed advanced chronic interstitial nephritis.

In uræmic cases of the cardio-renal type the estimation is perhaps most valuable. There is no increase in the non-protein nitrogen in chronic parenchymatous nephritis, nor in nitral disease with congested kidneys, but in "azotæmic" cases it is always high, though not necessarily in proportion to the symptoms. I have notes of a fatal case in a boy of eleven, with the non-protein nitrogen at seventy-five, but the normal non-protein nitrogen is low in children and this figure probably corresponds to about ninety in an adult. In adults the non-protein nitrogen may reach two hundred and seventy milligrammes before death, nearly ten times the normal.

Repeated examinations give valuable information as to progress in the less severe cases. In cases of prostatic disease I am informed that the non-protein nitrogen is of

importance, since the kidney efficiency often suffers and when this is the case prostatectomy is dangerous. If, however, the bladder is drained supra-pubically, a considerable degree of recovery may take place and the major operation can then be performed with safety.

It is remarkable that in a series of cases of acute pneumonia there was increased non-protein nitrogen, between forty and fifty milligrammes, doubtless due to toxæmic damage of the kidney.

THE ORIGINS OF RENAL INEFFICIENCY.

By T. Brailsford Robertson, Ph.D., D.Sc.,
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Those who uphold the modern theory of renal secretion, regard the capsule of Bowman as a passive filter which removes from the blood its proteins and formed elements, like many other filters with which we are familiar, and permits under normal circumstances the passage of all of the crystalloidal constituents of plasma into the cavity enclosed by the capsule and thence into the renal tubules. The fluid which enters the first convoluted tubule is therefore essentially deproteinized blood-plasma and, in order to provide the total normal output of urea, no less than sixty litres of fluid must pass into the convoluted tubules every twenty-four hours. This, however, only represents about 13% of the total blood supply to the kidney during the same period.

The force which accomplishes this filtration, is presumed to be the hydrostatic pressure of the blood which is delivered to the glomerulus by a very short path from the main arterial trunks. The maintenance of high pressure within the glomerulus is insured by the relative constriction of the glomerular orifice. Acting against this hydrostatic pressure we have the osmotic pressure of the colloidal constituents, chiefly the proteins of plasma, which amounts to some forty millimeters of mercury. Assuming the hydrostatic pressure in the glomerulus to be approximately equal to the mean arterial tension, then subtracting the opposing osmotic pressure, there remains an effective pressure of filtration amounting to between eighty and ninety millimeters of mercury.

Under this pressure the blood in the glomerulus is partially deprived of water and crystalloidal constituents and therefore when it issues from the glomerulus its composition is very abnormal. In particular the osmotic pressure of colloidal origin has been enhanced by at least 25% to 30% in consequence of withdrawal of water from the plasma, so that we may assume that the negative pressure due to the attraction of these colloids for water now amounts to not less than fifty millimetres of mercury.

This blood which is now distributed to the convoluted tubules, has lost much of its original hydrostatic pressure, in the first place by reason of its loss of volume and in the second by reason of the frictional resistance to flow which has to be overcome during its passage through the glomerulus. When therefore it enters the network of capillaries which surrounds the convoluted tubules, it may be assumed that the effect of widening the area of the circulatory bed, superimposed upon the previous loss of momentum, will have reduced the hydrostatic pressure to a low level, possibly even below that of the now enhanced osmotic pressure arising from its content of colloidal constituents.

To this blood of abnormal composition water is restored by the tubules, together with all of those constituents which are essential to render its composition normal. These constitute the "threshold" substances in urine, such as sodium chloride. Those constituents which are not requisite to the normal composition of blood, are either not returned at all through the tubular epithelium or else are very greatly concentrated and these constitute the non-threshold substances in urine, such as urea. Sugar (glucose) is generally regarded as a threshold substance, differing in its behaviour from sodium chloride merely in this, that whereas the concentration of sodium chloride in the blood which is delivered to the kidney, is usually above the threshold and a proportion of the sodium chloride is in consequence habitually excreted, the concentration of glucose in the blood delivered to the kidney is usually below the threshold and in consequence it is wholly returned to the blood through the tubular epithelium.

The evidence in support of this view has been summarized by Cushny and does not require recapitulation here. In the interpretation of physiological findings it has provided an eminently satisfactory solution, but in the interpretation of pathological events it has not been quite so satisfactory. It is this that constitutes the difficulty in deciding upon an ideal procedure for the estimation of renal efficiency. It is my purpose to show that by a single modification which however is of very far-reaching significance, the modern theory of renal secretion may be rendered no less adequate to interpret pathological events, so that the findings of physiology and morphological pathology may by this means be brought into satisfactory harmony.

Renal inefficiency is indicated by defective excretion of the normal urinary constituents, such as urea, uric acid and inorganic salts. In terms of the modern theory of urinary secretion such deficiency of output might be supposed to have arisen in either of two ways, namely, through deficient permeability of Bowman's capsule or through excessive permeability of the tubular epithelium, permitting abnormally extensive restitution of the urinary constituents to the blood. The great majority of modern authorities have unhesitatingly adopted the former alternative and the deficiency of renal output is thus attributed wholly to defective permeability of the capsule. If, indeed, we were to assume that the non-threshold constituents of the urine are not in any measure returned to the blood, then no alternative would be open to us and defect of such constituents in the urine must then unquestionably be attributable to diminished filtration through Bowman's capsule. This assumption, however, even if it were valid for the normal kidney, would not necessarily be valid when applied to the kidney which has been rendered abnormal by tubular lesions. We commonly suppose that the normal tubules are not permeable at all to urea and on the basis of this supposition we estimate that from sixty to seventy litres of deproteinized blood plasma must pass through Bowman's capsule to furnish the urea in a litre of urine. In com-

parison with urea somewhat over one half of the uric acid in this filtrate is returned to the blood. But there is no evidence that the tubules are completely impermeable to urea. Our estimates of permeability, based upon blood and urine analyses, are comparative and not absolute. Thus, if half the urea were actually returned to the blood in the normal kidney, then the total volume of fluid passed into Bowman's capsule would be one hundred and twenty litres per litre of urine and three-fourths of the uric acid contained in this plasma-filtrate would be reabsorbed in the tubules. Obviously any enhancement of the permeability of the tubules for urea or uric acid would in this event lead to the retention of these substances in the blood. Thus even phenol-sulphone-phthalein, which is not a normal constituent of the blood and is excreted with remarkable rapidity, may in the diseased kidney be returned to the blood through the injured tubules and thus perform a short-circuit which precludes or delays its issuance in the urine. Similar considerations apply to the other substances the output of which has been employed as a means of testing renal efficiency, such as urea, creatinin, lactose, phosphates and so forth.

There is one consideration, however, which appears to preclude the adoption of the view that deficient urinary output is due to the development of a renal short-circuit, and that is the absence of glucose from the urine of the majority of nephritics even in the most advanced stages of renal degeneration. It is obvious that if a renal short-circuit were in fact established the composition of urine would eventually approximate to that of deproteinized blood plasma, since no selectively permeable barrier would be present to overcome the osmotic forces which operate to restore identity of the composition of the contents of the tubule with those of the encircling capillaries. Deproteinized blood-plasma, however, contains about 0.1% of glucose and to this extent, therefore, glucose should appear sooner or later in the urine of every nephritic who displays tubular degeneration.

As a matter of fact, however, "renal diabetes" or more properly "renal glycosuria," that is glycosuria unaccompanied by hyperglycæmia, is an exceedingly rare phenomenon. Allen admits two cases which he considers have been effectively established in the literature which had appeared prior to his own investigations, and Allen, Wishart and Smith report three additional cases which they regard as veritable instances of renal glycosuria. Lewis and Mosenthal report another. Taking all the cases together and excluding those in which repeated blood-sugar estimations were not performed, there are not above a dozen established instances of renal glycosuria on record in the literature. In the three cases cited by Allen, Wishart and Smith slight impairment of renal function was indicated by the phenol-sulphone-phthalein test, but the extent of impairment was trivial in comparison with that which is frequently encountered in nephritis without any accompanying glycosuria. In this particular, therefore, there is no general tendency, excepting in cases of nephritis induced by poisoning with heavy metals such as uranium or mercury, for the composition of urine to approximate to that of deproteinized blood-plasma and we must assume, if glucose gains entry to the tubules through Bowman's capsule, that even in the most advanced nephritis the tubular epithelium which remains, is still sufficiently unimpaired to restore glucose in its entirety and against an osmotic gradient to the blood which is contained in the encircling capillaries.

If we adopt this alternative, however, and in accordance with prevailing opinion regard renal insufficiency as primarily of capsular origin, we are at once confronted with a series of instructive discrepancies between the histological and the chemical findings, for in chronic interstitial nephritis, accompanied by gross impairment of renal efficiency, much microscopically visible injury has usually been sustained by the epithelium of the tubules and the capsules may not infrequently appear comparatively uninjured. It may be contended with much reason that the thickening and increased density of interstitial tissue and the consequent impairment of the blood-supply to the tubules which usually accompanies this condition, must delay interchange of water and dissolved substances between the tubules and the circulation, so that even if the permeability of the tubular epithelium is actually increased by denudation, this would be compensated to the extent that interstitial thickening has occurred. There is, however, one profound difference between this sort of impermeability and the normal impermeability of the tubular epithelium for non-threshold substances and it is this, that the impermeability due to mere thickening and density of tissue not specially organized for secretory activity cannot be supposed to be selective. It might lead to diminished return of water and dissolved substances to the blood, it is true, but to the degree that they are restored at all they must be restored in proportion to their respective osmotic pressures and the composition of the residual fluid which will be voided as urine, must therefore tend to approximate more and more closely to that of deproteinized blood-plasma, as this type of impairment progresses. Among other constituents deproteinized blood-plasma contains sugar, so that in any event denudation of the tubular epithelium should lead to the appearance of sugar in the urine.

Cushny disposes of this difficulty by deprecating all attempts in the present condition of our knowledge to correlate histological and chemical findings, implying by this that functional and morphological impairment need not necessarily proceed hand in hand. In other words he supposes that a microscopically minor injury to the capsule may be physiologically more important than a microscopically prominent injury to the tubules. This standpoint is of great value in that it draws attention to an undeniable possibility which is only too likely to be overlooked by the professional morphologist. Nevertheless, even if we adopt it unreservedly, it fails to afford an intelligible explanation of the nature of that impairment which renders a filter of fragile protoplasm more able than before to sustain hydrostatic pressure or, alternatively, endows it with a capacity which formerly it did not possess, the capacity namely of filtering crystalloids out of their solution in blood-plasma. In other words the injury is of such a nature that the capsule is strengthened and rendered more impervious than before. It is exceedingly difficult to conceive any injurious process which could

lead to such a result without proliferation and the production of new barrier against filtration. On the other hand microscopic inspection of the kidney of a chronic nephritic forcibly suggests that at numerous points within the tubules a renal short-circuit may have been established. By the establishment of a renal-short-circuit it must be understood that I do not mean mere leakage of fluid due to interruption of the continuity of the tubular lining, but loss of the capacity of selective restitution to the blood consequent upon injury to the functional efficiency of the tubular epithelium. The structure of the cells composing the tubular epithelium is very elaborate and we cannot suppose that this complex architecture is devoid of purpose or utility. We do not speak of a bisected heart as retaining half the efficiency of a whole heart. It is obvious that it can retain no efficiency at all. Why, then, should we assume that a partially denuded renal epithelium retains so much of its original efficiency as to be able to restore glucose quantitatively to the blood against an osmotic gradient?

It is not denied that diminution of the permeability of the glomerulus or the capsule may occur in consequence of proliferative changes, as for example in chronic glomerular nephritis. But these are precisely those instances of renal disease in which retention of water and sodium chloride is observed. Now the sodium chloride in normal urine is only slightly in excess of the sodium chloride in plasma. In other words, sodium chloride is normally returned very freely to the blood through the wall of the tubule. Damage to the tubular epithelium would, therefore, not greatly affect the sodium chloride content of urine, while capsular impermeability might decidedly interfere with the output of both sodium chloride and water. In chronic nephritis with extensive tubular lesions and little visible glomerular change, reduction of sodium chloride output is not a characteristic feature of the condition although, of course, with lapse of time a considerable degree of retention of sodium chloride in the blood may occur, owing to the establishment of the renal short circuit and the consequent sustained absence of the normal small excess of concentration of sodium chloride in urine as compared with its concentration in plasma.

When one alternative leads us to irreconcilable discrepancies between theory and observation, the remaining alternative invites renewed consideration. May we suppose that renal inefficiency in chronic interstitial nephritis is due not wholly to loss of permeability of the capsule, but in greater or less degree to the establishment of a renal short-circuit, whereby a considerable proportion of the normal urinary output is restored to the blood through the damaged walls of the convoluted tubules? We have seen that the sole obstacle to the adoption of this hypothesis which would effectively reconcile the chemical and histological findings, is the fact that whereas glucose does appear in the urine in the condition of hyperglycæmia which accompanies diabetes, yet it does not appear in the urine of otherwise normal persons who are affected with most extensive tubular lesions arising from chronic interstitial nephritis.

If, then, we adopt this alternative, we are forced to assume that in the non-diabetic individual the blood glucose does not penetrate either Bowman's capsule or the injured tubular wall, in fact as if it were non-diffusible. In the diabetic individual on the contrary the blood sugar or that part of it at all events which is responsible for the hyperglycæmia, is diffusible and consequently appears in the urine.

We have so far directed our attention wholly to renal events. In the endeavour to interpret these we have been led to a conception of the condition of blood-sugar which was proposed long ago by Pavy and Lépine and has been revived in recent years by F. M. Allen. It is a familiar fact that glycosuria in diabetes is accompanied by extensive polyuria and it has been supposed that the presence of glucose in the lumen of the tubules necessitated a high output of water, owing to the steep osmotic gradient which opposes the return of water to the blood. If hyperglycæmia is artificially induced in normal animals by the intravenous injection of massive doses of glucose, the glycosuria which ensues, is similarly accompanied by polyuria. It has been shown, however, by F. M. Allen that if the glucose is administered by any other route than by intravenous injection, if it is administered orally, subcutaneously or intramuscularly, then quite a different result is obtained. The hyperglycæmia results in glycosuria, but instead of polyuria oliguria accompanies this glycosuria. The secretion of urine is scanty, excessive thirst is experienced, but the fluid thus taken in is retained until the glycosuria has ceased and the glucose in the blood has sunk to the normal level. The whole of the stored up water is then released with relative suddenness and pours forth through the kidneys. In other words in the normal individual glucose which has gained entry to the blood by passage through tissue behaves towards the kidney as if it were a colloid and non-diffusible, so that it contributes to enhance that part of the osmotic pressure of the plasma which is of colloidal origin and to diminish the effective pressure of filtration, that is the excess of hydrostatic pressure over osmotic pressure of colloidal origin. In the diabetic individual the reverse is the case. Glucose administered by any channel arrives in the blood in the normal diffusible form and consequently appears in the urine together with the water necessary to reduce its osmotic pressure to a level withstandable by the epithelium of the tubules.

Notwithstanding these striking and otherwise it would seem inexplicable observations it is generally assumed in current bio-chemical literature that the view that glucose in the blood of the normal individual is bound up in some non-diffusible complex is obsolete and untenable. On analysis the evidence which has led to the rejection of the older view revived by Allen, appears to amount in the main to this, that when specimens of blood are dialysed against glucose solutions of various concentrations, the only solution which leads to no alteration of the glucose content of the blood, is that which contains the same initial concentration of sugar. It is concluded from this that the whole of the glucose in blood is present therein in a diffusible condition. This conclusion is open to a variety of criticism, however, and it is not nearly so easy as it may appear to define beyond question the physical condition of a substance which is dissolved in a complex

and unstable fluid such as blood. Moreover, it should not be forgotten that in order to gain entrance to the uriniferous tubules the blood sugar must pass through not one but two membranes, the wall of the glomerular capillary that is and the membrane which forms the enveloping capsule. Experiments by Mr. A. B. Anderson in this laboratory which are not yet completed, indicate that the glucose present in normal blood is diffusible, but that after issuance from the dialysor and its consequent separation from the colloidal constituents of the blood it undergoes polymerization. This polymerization, if it occurs in the kidney, may possibly render the glucose unable to traverse the second membrane which intervenes between the blood and the lumen of the tubules.

If we review the evidence which points to the passage of normal blood glucose through Bowman's capsule and its quantitative reabsorption by the tubules, we find that it is scanty and inconclusive. Thus G. A. Clark has shown that in the frog in which the tubules receive a double blood-supply from the glomeruli and from the renal-portal system when the renal arterial and renal-portal vessels are simultaneously perfused with Ringer's solution containing glucose, no glucose appears in the urine until the concentration of glucose in the perfusion liquid exceeds 0.052%. If the perfusion liquid contains less than 0.23% of glucose, the urine which is passed, always contains from 0.05% to 0.06% less glucose than the perfusion fluid. If the concentration of glucose in the perfusion liquid exceeds 0.23% then the kidney allows the whole of the glucose to escape into the urine. If, however, the glomeruli are perfused through the renal artery with Ringer's solution containing less than 0.1% or even less than 0.052% of glucose, the whole of this sugar will appear in the urine, provided the glomeruli are simultaneously perfused through the renal-portal with a glucose solution of such strength as to render the concentration of glucose in the mixed venous outflow in excess of 0.23%. Control experiments showed that sugar could not pass from the renal-portal circulation directly into the tubules. It is obvious, however, that these experiments throw no light at all upon the normal behaviour of blood sugar, because, as Allen's experiments show, glucose added to blood and still more, of course, glucose which has been added to a perfusion liquid, behaves towards the kidney like a foreign crystalloid, while the glucose which is normally present in the blood and which has gained access thereto by passage through tissue, behaves towards the kidney like a colloid.

Then we have the experiments of Nishi who compared the amount of sugar in the renal medulla and cortex in dogs, cats and rabbits, killed by bleeding and found that while the cortex contained 0.011% to 0.066% of sugar, the medulla was either entirely free from sugar or contained only a trace. This is held to indicate that the sugar found in the cortex is present in the capsules and disappears from the tubules in consequence of its reabsorption into the blood. But a closer scrutiny reveals the fact that this experiment, if interpreted in this manner, proves almost too much, since it becomes necessary for us to suppose that the whole of the reabsorption of sugar occurs in the proximal convoluted tubule, for if sugar were to escape absorption there it would pass on into the loop of Henle and so appear in the medulla. Now it must obviously be more difficult to absorb sugar from a dilute solution against an osmotic gradient into the blood than to reabsorb it from a concentrated fluid in which the osmotic gradient would be diminished or even until the last stages of absorption reversed in sign. It would obviously be a great economy of effort to reabsorb the water first or at any rate to reabsorb glucose and water together. But if water and glucose are both absorbed in the proximal convoluted tubule we can hardly avoid assuming that sodium chloride and other constituents of the blood-filtrate are reabsorbed here also and in that event what operation is left for the distal convoluted tubule to perform? Either we must assume that the renal tubules reabsorb sugar in the most wasteful and difficult manner with maximal expenditure of energy or else we must assume that the distal convoluted tubules are practically devoid of functional utility and represent merely a sort of insurance against occasional failure of the proximal convoluted tubules to perform their duty. In my opinion the analytical results obtained by Nishi may be susceptible of quite another explanation to that which he has offered, but it would be premature to dwell upon possible alternatives until much more experimental evidence bearing upon these phenomena has been obtained.

Recent accessions to our knowledge of carbo-hydrate metabolism have shown us that the glucose present in normal blood is not identical with the glucose with which we are ordinarily familiar. It is much more susceptible to oxidation and, as Winter and Smith have shown, it is possessed of a lower optical rotatory power than normal glucose. In the blood of a diabetic on the contrary the optical rotatory power of the sugar is normal or even in excess of normal. Without entering into a consideration of the unsettled question whether or not the glucose in normal blood represents a stereo-chemical modification of ordinary butylene oxide glucose, it is sufficiently evident that glucose in normal blood differs fundamentally in its chemical behaviour and optical properties from ordinary glucose. Among those particulars in which it differs from ordinary glucose, it appears that we must include its inability to penetrate the capsule of Bowman. It is not necessary at this stage to specify more particularly the origin of this peculiarity of the behaviour of blood glucose. The hypothesis of Pavy, Lépine and Allen may eventually prove to be correct or it may not. But the assumption that the glucose in normal blood differs from the glucose in the blood of a diabetic in its inability to traverse the capsule of Bowman appears to afford the only means of reconciling the modern theory of renal secretion with the histological and chemical findings in chronic nephritis with predominantly tubular lesions, for it enables us to trace the renal inefficiency which accompanies this condition, to the source which the histological appearances suggest, namely the establishment of a renal short-circuit.

I am greatly indebted to my colleague, Professor J. B. Cleland, for valuable criticism and advice which has materially assisted me in the preparation of this address. He is in no degree to be held responsible, however, for the personal opinions and theoretical views which I have ventured to put forward herein.